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PREVENTIVE MEDICINE IN BRITAIN

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Preventive medicine in Britain was first concerned chiefly with environmental hygiene. The years 1875 to 1900 covered a long series of progressive reforms under the direction of the Local Government Board, which supervised such local government as related to public health and relief of the poor.

These reforms comprised general sanitary improvements, pure water supplies, pure food supply, provision of isolation hospitals for infectious diseases, public vaccination, the supervision of slaughter-houses and common lodging-houses, and others. Local authorities obtained control over housing, powers to condemn slums, and to provide new housing accommodation. Infectious diseases were made notifiable, while port sanitation prevented the admission of fresh disease and plague and pestilence into Britain.

These measures were followed by a great improvement in Britain's national health. The water-borne diseases have become almost negligible. Cholera has been abolished and typhoid is now a rarity, though watch is still kept for epidemics caused by "carriers." Personal cleanliness and lessened overcrowding have stamped out typhus, the deadly "jail fever," which spread from the prisoner in the dock to the judge on the bench. Every second person is no longer scarred with smallpox.

The great advances made in medical and natural science contributed largely to administrative progress. For this was the age of Darwin, Huxley and Lister, of Pasteur, Simpson and Koch, of Stephenson and Watt, the first who ever burst into those silent seas of knowledge and revealed new learning in biology, antiseptic surgery, bacteriology, anesthetics and engineering science. The skill and experience of many have all been assembled to constitute the science of public health.

The succeeding trend of preventive medicine from the reign of King Edward VII onwards has been in the direction of preventing the contraction and transmission of disease in human beings. Progress in environmental hygiene has not stood still. There have been a number of Housing and Town Planning Acts and factory legislation.

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From 1919 to 1938 the number of new State-aided dwelling houses was about 1½ million, and private enterprise, without subsidy, produced nearly 2½ million houses, so that 4 million new houses have rehoused about one-third of Britain's whole population. The housing policy of the State has a three-fold objective: (1) the eradication of the slums; (2) the abatement of overcrowding; and, (3) the provision of new houses at as low a rent as possible.

Workers in mines and factories now pursue their avocations in a healthier atmosphere; there is less risk of disease, crippling and death; and lead and other forms of poisoning in industrial processes, as well as silicosis, have been greatly diminished.

Preventive medicine in Britain enlarged its activities some 30 years ago by taking the individual in hand, by promoting facilities and education for keeping him healthy, and by treating his disease in order to safeguard the community.

The State made an important contribution to this wider interpretation of public health by introducing school medical inspection in 1907. Medical inspection of school children has separated the impaired and defective child from the normal and healthy. Arrangements have been made for attending to the health of both sick and healthy children. Many morbid conditions have been reduced, the general physique of school children has improved, and in addition to direct medical results, the teaching of hygiene and cleanliness, the physical training and the provision of milk and school meals have reformed the physical condition of the children of Britain beyond all comparison with the past. A health conscience is developing both in the children and their parents.

During the past 30 years the larger authorities—the counties and county boroughs—have been given much greater powers as guardians of the public health. They were made responsible for the individual health services, the maternity and child welfare services (for the most part), the public assistance medical service for necessitous persons, the tuberculosis and venereal diseases services, the cancer service, the orthopedic service, the hospital services (including, to some extent, pathologic services), and the mental hospitals service.

Britain's Ministry of Health initiated these services by promoting legislation which made them a duty of the county councils and county borough councils, and by administering Government Grants to aid them. The cost of the services is thus defrayed partly by the State and partly by local rates. The Ministry lays down the lines on which these services are administered by the local authorities, approves the scheme of work, inspects the services through its medical officers, and by health surveys sees that a proper standard of efficiency is maintained, having regard to the individual authority's resources and needs. But the actual work is done by the county council and the county borough council with the advice of their medical officers of health.

Britain's National Health Insurance Medical Service, set up in 1911, is of primary importance in confirming the rôle of the medical practitioner as the first line of defense in combating disease. Normally, some 17,000 medical practitioners in England and Wales are engaged

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in this health service. It provides a means whereby the industrial workers of the country can have ready access to medical advice, not only for actual ill health, but for those who need guidance to keep their health. The Service is administered centrally by the Ministry of Health and locally by Insurance Committees.

In Wales the Welsh Board of Health is part of the Ministry of Health, while the Department of Health for Scotland exercises similar functions to those of the Ministry.

Two world wars seemed likely to set back the hands of the clock of social progress in Britain. But let us look at some comparative vital statistics. The death-rate for England and Wales about the year 1900 was 18 per 1000, whereas since 1918 it has been in the neighborhood of 12 per 1000. In 1938, the last unbroken year of peace, it was 11.6 per 1000 persons.

Tuberculosis is a disease whose ravages are prone to affect the youthful and adolescent as well as the adult members of the population. The death-rate from tuberculosis serves as a convenient index of the success of public health measures. At one time tuberculosis occupied first place among the principal epidemic or general diseases as a cause of mortality. It has fallen from that disgraceful pride of place. During the 25 years before 1936 the standardized death-rate from pulmonary tuberculosis declined by 49%, and for non-pulmonary tuberculosis by as much as 69%.

The crude death-rate from all forms of the disease was 635 per million, the lowest figure yet recorded. In the decade 1911 to 1920 the number of deaths each year from tuberculosis (all forms) was about 52,000, "a thousand funerals a week." In 1938 this figure was only 26,176, or nearly half the average figure in 1911 to 1920.

In the period 1896 to 1900 the infant mortality-rate (that is the death-rate of infants under 1 year of age per 1000 born) was 156. In 1938 it dropped to the then record figure of 53.

The maternal mortality-rate, which for many years had averaged over 4 per 1000 live births, began to decline in 1936 and by 1938 had reached the then record figure of 2.97. This fall coincided with special measures undertaken for the care of women in childbirth and with special chemotherapy for puerperal sepsis.

These are salient examples of the improvement in national health brought about by preventive medicine. In 1939, when Britain was forced into totalitarian war, the people marched into battle fortified by better physique and better health, the gifts of medical and public health progress.

War favors disease, and the task before the State and health authorities both before and in the early years of the war was a stupendous one. Important and extensive as public health responsibilities were during the last war, they are vastly increased in the warfare of today. The discoveries of science have placed more powerful weapons of destruction in the hands of man. The aeroplane flies bearing death between its wings. The cities of Britain are no longer cities of refuge for invalids, women and children, but may become the most vulnerable centers of attack.

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War also exposes populations to the risks of famine and malnutrition, to liability to the contraction of infectious diseases and epidemics through overcrowding, movements of population, increased fatigue and lowering of bodily resistance, and grave apprehensions were expressed that the national health would seriously deteriorate.

With those fateful considerations in mind, the British Government had to take important measures of protection, as well as maintaining the public health services and adapting them to war conditions. Two important measures were the organization of an emergency medical service for the treatment of air-raid casualties and of the wounded, in itself a stupendous task, and the evacuation scheme which included the transfer of school children, expectant mothers, young children, cripples, and blind persons from urban centers to other areas less exposed to German air-raids.

These war schemes at first were far from perfect. In the light of after-events it can be seen that many mistakes were made, many unnecessary plans were devised and there was much waste of effort in preparing for eventualities which never arose. These defects were practically inevitable in a new organization and certainly inevitable in a war which has taken a course very different from the campaigns of the past.

On the whole, however, they met with great success. This was due to careful central planning, to continual overhauling of the machine, and above all to the loyal coöperation of doctors, students, nurses and hospital and social workers of every kind. Britain's Medical Research Council in conjunction with the Ministry of Health set up a comprehensive laboratory service throughout the country. They are also making investigations into war problems of disease such as burns, gas gangrene, blast injuries and others.

Under the capable shield of the allied navies the food supplies of the country are being maintained and the present scale of rationing is equitably administered by the Ministry of Food and is fully adequate for good nutrition.

The prevention of scurvy, scurvy rickets, rickets and other deficiency diseases is included in the economic defense of Britain. Due provision is being made for milk for children and expectant mothers, school meals for children and communal feeding centers. Under the Ministry of Labour and National Service, industrial health is being maintained in factories and workshops with advances in medical and welfare services.

The vital statistics of Britain on the whole continue to be satisfactory. The decline in infant and maternal mortality has been maintained. Two evils, tuberculosis and venereal diseases, both "camp-followers of war," have given some cause for anxiety, but further special measures have been organized to combat them. There have been no large epidemics and any outbreaks that arise are promptly tackled by the health authorities. Diphtheria is still too prevalent, the campaign for immunization against that disease is being urgently pressed and with success.

The sulphonamide preparations are in general use and have reduced the mortality from pneumonia, cerebrospinal fever, puerperal fever

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and other diseases to a remarkable degree. Encouraging researches are proceeding on the application of *Penicillin* to war wounds and disease. In brief, British preventive medicine is not only achieving a remarkable and unprecedented success in the present war, but its scope and range are being extended.

It is an encouraging sign of confidence in victory that while Britain is engaged in a life or death struggle for freedom, she can still find time for future planning in public health.

The defects and limitations of the present system are realized, however, and numerous schemes and plans are being ventilated both officially and unofficially. It is the Government's declared intention to fulfill the intentions of Assumption B of the Beveridge Report by establishing a comprehensive medical service. It seems an inevitable condition of such a service that it should be closely associated with the public health services of Britain's local authorities.

For health is more than a question between doctor and patient, valuable as is this relationship. The environment and social conditions of the patient need full attention and preventive medicine must employ a social armamentarium as well as a medical one in order to maintain and improve the public health.

This means a marshaling of all forces—medical, environmental, social and individual to prevent and to combat disease. A notable means to this end is the recent establishment of Chairs of Social Medicine at the Universities of Oxford and Birmingham. Another is the work of the Central Council for Health Education in educating the community in hygiene and the avoidance of disease.

A comprehensive medical service is to be established and a White Paper on the subject just has been issued by Britain's Minister of Health. It may be observed here that the nuclei of such a service are already present in the Insurance Medical Service, the Public Assistance Medical Service, the health services and hospitals of the local authorities, the voluntary hospitals, the specialist provision made by municipal and voluntary agencies and the planning of the Emergency Medical Service. The task is to combine this scattered provision into one harmonious whole. In all these schemes of reform many complicated problems are presented which time, patience and experiment will solve.

CAPILLARY PERMEABILITY IN MYXEDEMA*

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The presence of edema in the skin of patients suffering from myxedema and the tendency to generalized serous effusions are so far physiologically unexplained. The fact of their presence has been stressed by many observers. The tendency to serous effusions, espe-

* Aided by a grant from the John and Mary R. Markle Foundation.

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cially in the pericardial cavity, has even impressed many observers so much as to cause them to deny any genuine enlargement of the heart itself, attributing all roentgen evidence of enlargement to pericardial effusions. Feasby[2] describes a case in which he was able to measure the intrapericardial pressure and to withdraw repeatedly large amounts of fluid from the pericardium. Marzullo and Saverio[13] describe a case with multiple serous effusions and cardiac involvement which returned to normal after treatment with thyroid. The heart also became considerably smaller after treatment. Lehrman, Clark and Means[11] report 5 myxedema autopsies, 4 of which showed *interstitial* edema of the heart muscle and only 2 increased fluid in the pericardial sac. They summarize their findings of the typical pathology as found in myxedema as follows: (1) interstitial edema; (2) fibrosis; (3) pericardial effusion. Hurxthal[6] also reports cases of myxedema heart with congestive heart failure and polyserous effusions. He states definitely that he attributes the edema to the basic myxedema and not to the subsequent heart failure. Similar findings are reported by Hanssen.[5] On the other hand, it can be considered well established that the blood flow in the periphery of myxedema cases is considerably diminished. In their extensive studies, Stewart, Deitrick and Crane,[17] Zondek,[20] Stewart and Evans,[18] and Macy and co-workers,[12] state that the circulation time in all cases of myxedema is prolonged and that the flow of blood through an extremity is markedly decreased. All these changes return to normal after proper treatment has been instituted. No unanimity can be found in the literature concerning the meaning of the changes in the electrocardiogram. All authors state that there are marked changes in the T waves and occasionally of the P–Q interval in connection with the more or less pronounced general lowering of the voltage. Most of the authors are inclined to attribute the T wave changes to arteriosclerosis, as can be expected with the high cholesterol in the blood; and the changes in voltage to the formation of small or large effusions in the pericardium. Only Lehrman[11] and his co-workers state that in all probability the interstitial edema is the main cause for the electrographic changes. Recently, Zondek, Michael and Kaathz[20] very clearly stressed the point that the interstitial edema of the heart muscle is, in the majority of cases, the cause for the anginal syndrome. They explain it by the statement that the edema is pressing on the blood-vessels, a contention which one can hardly follow; for the tissue pressure can physiologically never be higher than the pressure in the vessel leading to the area.

A very remarkable finding is published in the literature. Thompson, Thompson, Silveus and Dailey[18a] found that in myxedema the protein content of the spinal fluid was nearly always markedly increased (up to 242 mg.) and that the globulin test was always positive. The pressure was very often markedly increased. All these findings return promptly to normal on thyroid therapy. They were at a loss to explain these results.

Observers of the capillary microscopic picture in this disease agree that the number of visible capillaries is low.[14,20]

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Starling,[16] in his monograph, "The Fluids of the Body," summarizes the factors causing increased transudation:

A. Increased intracapillary pressure: (*a*) venous obstruction; (*b*) vasodilation; (*c*) plethora.

B. Increased permeability of the vessel wall: (*a*) local injury by mechanical irritants; (*b*) local injury by thermal irritants; (*c*) local injury by chemical irritants.

C. Watery condition of blood (hydremia).

D. Increased molecular concentration of the tissues.

Considering the factor of increased capillary pressure, there is no reason to assume that it is present in myxedema, especially not to an extent as to explain the findings described below. Venous pressure measurements as carried out by Golden and Brauns[4] have not shown any increase in venous pressure, a finding which is in accord with our own observations. Neither vasodilatation nor plethora is present in myxedema, nor is there any reason to assume a marked hydremia in this disease.

In doing circulation time determinations in patients with myxedema (by means of the fluorescein method reported elsewhere),[8] it became apparent that these patients had an especially rapid and intense staining of the tissue cells by the dye. Since these patients had a prolonged circulation time and, since we were able to show that in the presence of a normal capillary permeability, slow circulation times were identical with *slow* staining of the tissue cells due to the diminished amount of dye brought to an area, this rapid and intense staining in myxedema patients seemed so remarkable that it stimulated us to the study herein described.

Three attempts have been made so far to attribute the serous effusions in myxedema to changes in capillary permeability. Neither Gänszlen[3] and Peterson[15] with the blister method, nor White and Jones[19] with the pressure plethysmograph have succeeded, however, in proving this assumption. It is probable that in these studies the methods used were not adequate for this purpose and the range of the normal was so wide that no positive results could be expected.

In order to make our observation objective and to be able to estimate its magnitude, recourse was taken to the following method.

Method. The Dermofluorometer,* which is described in detail elsewhere,[10] was used for these observations (Figs. 1 and 2). This device consists of a small but intense light source which, by means of proper filtering radiates a blue light of a short wave length (around 4000 Angstrom units). This light source is rigidly aligned at an angle of 90 degrees to the opening of a sensitive phototube which, in turn, by means of proper filtering, picks up only light waves in the region of green, that means in the region of the fluorescence of fluorescein. The light source as well as the phototube are at a constant distance from an opening in a bakelite plate through which the light shines on the skin of the patient and from which the reflection is picked up by the phototube. The changes in the current output of the phototube, which are dependent upon the fluorescent radiation, are amplified and registered on a measuring instrument. This instrument is calibrated in such a way that an alkaline

* Manufactured for us according to our specifications by the Photovolt Corp., New York City.

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fluorescein solution of a concentration of 1 to 30,000,000 in a cuvette of glass permeable to ultraviolet and of 5 mm. depth gives a deflection of one division. This deflection is called *one fluorescein skin unit.*

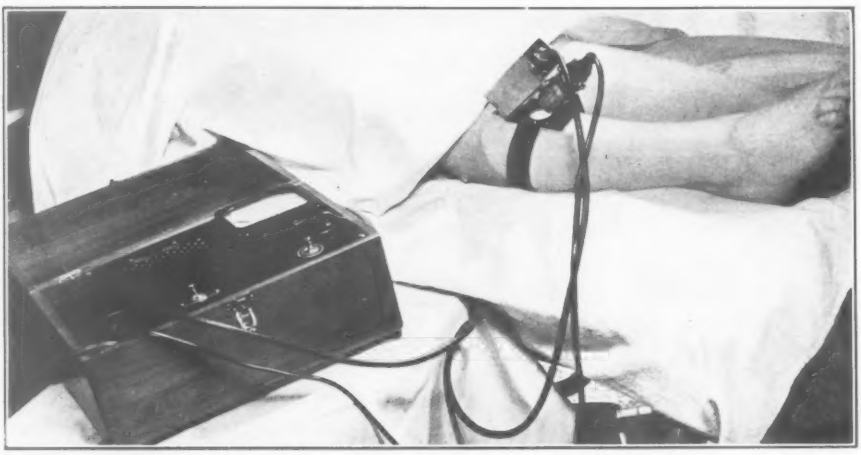

FIG. 1.—The Dermofluorometer attached to the leg of a patient. The search unit is on the skin, the registering instrument on the table.

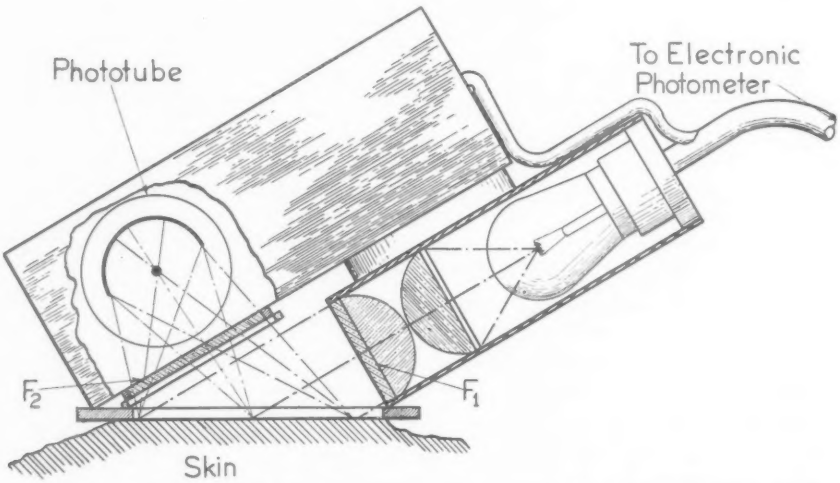

FIG. 2.—The principle of the Dermofluorometer. The light source radiates through the blue filter, F_1, on the skin. The fluorescence of the skin produced by the intravenous injection of fluorescein is registered by the phototube. Filter F_2 prevents all light except green-yellow from reaching the phototube.

The patient rests for at least 15 minutes before examination in a room with a temperature between 75° and 80° F. Before the examination is carried out, several test spots on the body of the patient are tested with this instrument in a dark room for their illumination. Since the skin in some individuals has a somewhat greenish color, before the injection of any dye these so-called background readings are necessary to eliminate errors. The very low values are noted and later deducted from the values found after the injection of the

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fluorescein. One and three-tenths cc. per 10 kg. of body weight of a 5% fluorescein solution to which 5% of sodium bicarbonate has been added are then injected intravenously. The first 4 cc. are given very rapidly while the rest is given within 90 seconds. It may be stressed here that this fluorescein solution is optically 22% more active than a solution of *sodium* fluorescein. The dermofluorometer is attached to the leg of the patient by a rubber strap, while a long wave ultraviolet reflector, such as used for the determination of the circulation time,[7,9] is beamed on the lips of the patient. Thus the circulation time to the lips and to the leg is being determined objectively.

The degree of deflection registered by the dermofluorometer at the different test spots is read in the beginning every 2 minutes and later every 5 minutes.

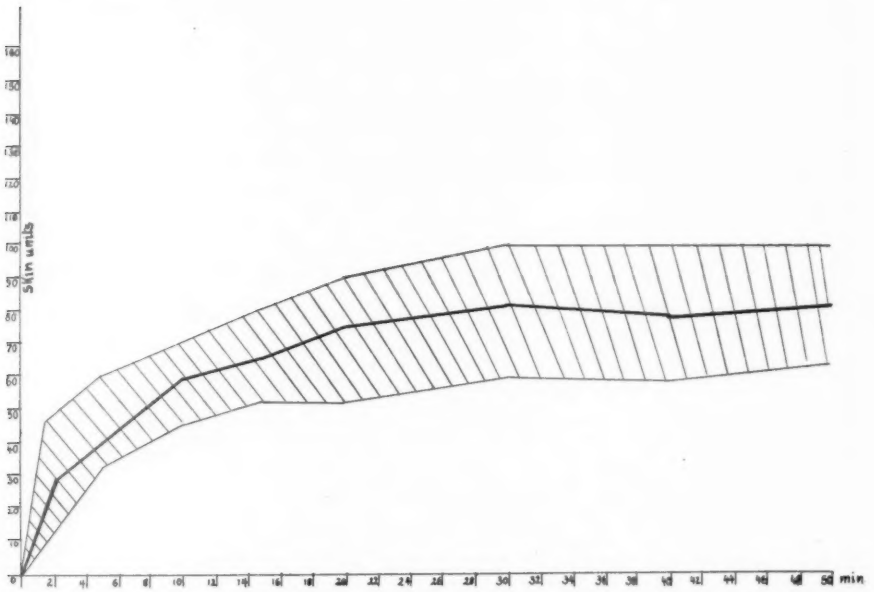

FIG. 3.—The fluorescence values obtained from the legs of 20 normal individuals after the injection of fluorescein. The heavy line in the middle represents the average, the upper and lower border lines, the possible variations in normals.

A curve is thus obtained which is mainly dependent upon 4 factors: (1) the number of capillaries per square inch; (2) the amount of blood streaming through them per time unit; (3) the capillary permeability; (4) intracapillary pressure.

Fluorescein is a very small molecular dye (mol. weight 332). It penetrates practically immediately from the capillaries into the tissue, as can be easily observed under the capillary microscope. It diffuses over the entire length of the capillary loop. In ultrafiltration experiments which represent the experimental counterpart to capillary filtration, it can be shown that three factors influence the amount of fluorescein obtained in the filtrate (tissue fluid): (1) the pore size of the filter (capillary permeability); (2) filtration pressure (capillary pressure); and (3) concentration (blood concentration).

The curves of normals obtained with this method are in a very close range. It was astonishing to see how rigidly the body adheres to its

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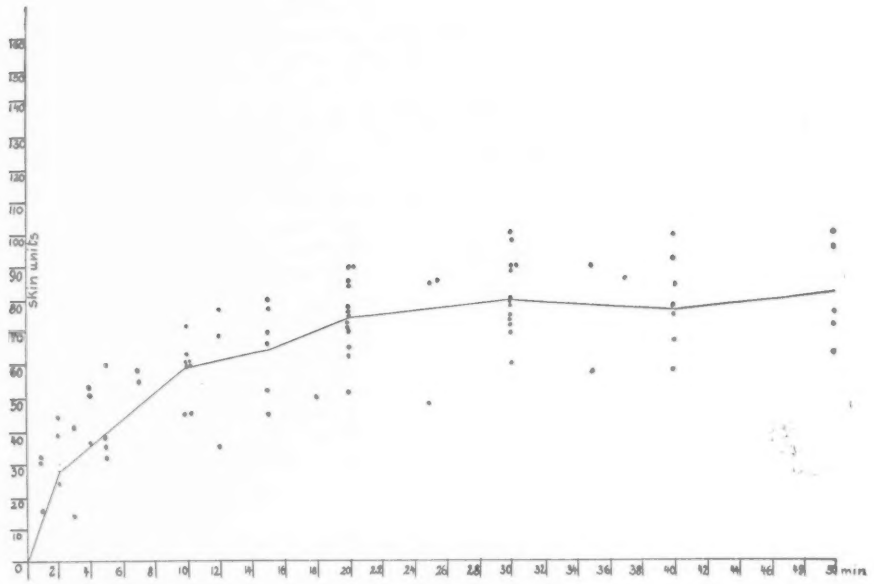

FIG. 4.—The scattering of the values in the permeability curve of 20 normal individuals.

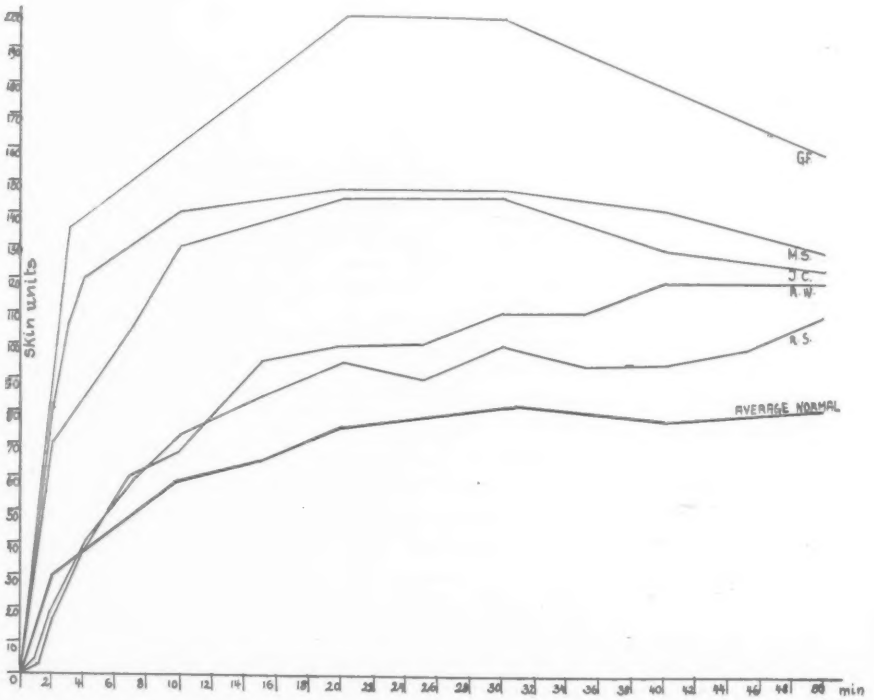

FIG. 5.—The permeability curve as obtained in 5 cases of myxedema after fluorescein injection. The heavy line represents the average normal curve.

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permeability curve. We have repeated curves as often as 4 times in the same person at short and long intervals and always observed values within range of ± 5%. Figure 3 shows the average curve for the normal persons (20 persons). The upper and lower border curves represent the borders of the normal. Figure 4 gives the scattering of the values obtained in these 20 normal persons.

Nine cases of patients in cardiac failure with severe edema showed all curves within normal limits.

Three cases of severe edema in the lower part of the body due to cirrhosis of the liver showed normal curves in all regions.

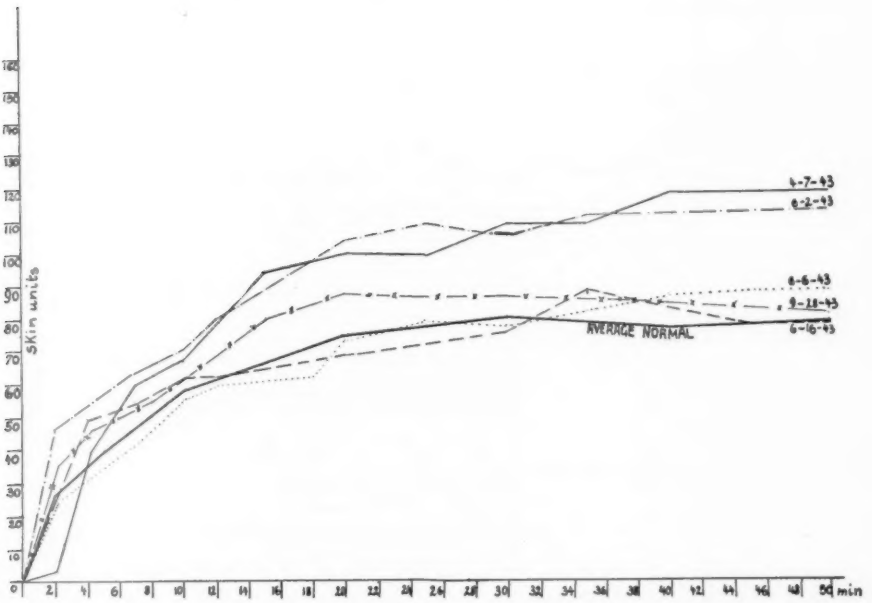

FIG. 6.—The permeability curves of Case R. W. before and after treatment with thyroid. The heavy line represents the average normal curve.

Two cases of severe undernutrition with vitamin deficiencies and generalized edema showed very high fluorescein permeability curves. The most obvious increase in capillary permeability can be noticed in inflammatory reactions. At the side of such a lesion the dye seems to pour out of the capillaries and the area is markedly increased in its fluorescence as compared to the surrounding tissue.

Five cases of myxedema, all in women, were observed. All these cases had a markedly increased fluorescein permeability curve before treatment was instituted. Figure 5 shows the curves obtained from tests on the legs of these patients when they were first examined. It may be stressed here that the curves of all other test spots of these patients were also far above the normal for the regions concerned, and that the leg curves are only chosen as an example since our experience for this test spot is the widest. In 4 cases the circulation time was

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more or less prolonged. Table 1 shows all the essential data for these patients at their entrance into the hospital. In all cases the electrocardiogram showed very low T waves in all leads; in 3 of the cases low voltage was present. The heart was markedly enlarged in 3 cases and moderately enlarged in 2. We were able to follow 2 of the cases throughout their clinical course until they returned to a normal basal metabolism with a complete disappearance of the signs and symptoms. Two of the patients left the hospital prematurely to return to the care of their private physicians and could not be followed further; while 1 patient died from coronary occlusion before intense treatment could be started. The B.M.R. was very low in all cases, and the cholesterol and plasma proteins high in all of them.

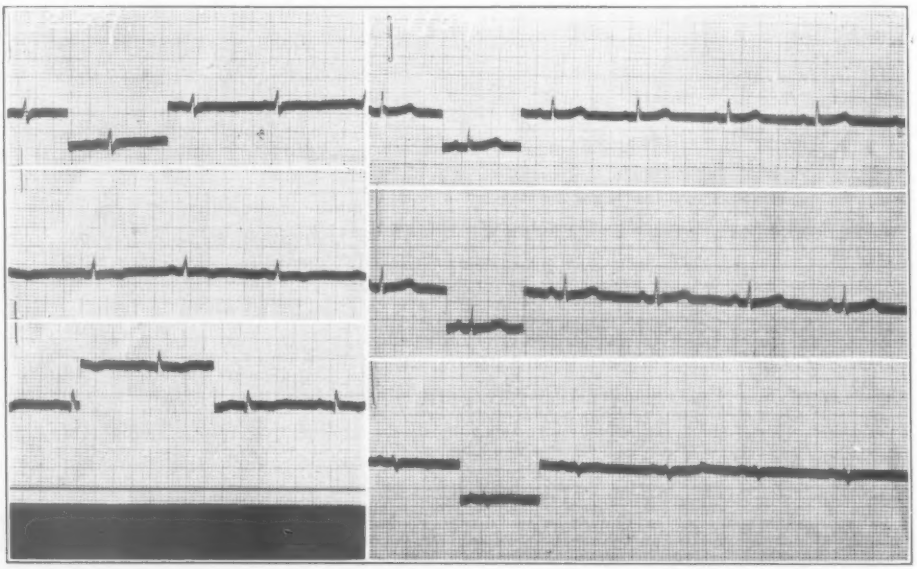

FIG. 7.—The electrocardiogram of Case R. W. before and after treatment with thyroid at the time of high and normal capillary permeability respectively.

In the 2 cases which we were able to follow throughout their clinical course, the permeability curve returned gradually to normal with the increase of the basal metabolic rate and the return of the ECG to normal. One of these cases, which seems to show the clinical course and its relation to the capillary permeability is clearly represented in Table 2 where all pertinent clinical data are entered. The ECG's before the therapy and after return of the basal metabolic rate and permeability curve to normal, are shown in Figure 7. Figure 6 shows the permeability curves as obtained from this patient at the time when the clinical findings as mentioned in Table 2 were present.

Discussion. Finding an abnormally high fluorescence of the skin after the injection of the small-molecular dye fluorescein in cases of myxedema can only be explained by a high capillary permeability. The argument that the skin of the patient with myxedema may have a

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TABLE 1.—ESSENTIAL DATA OF PATIENTS UPON ENTRANCE TO THE HOSPITAL

No.	Name	Age	Date of exam.	B.M.R.	Circ. time: Arm to lips (sec.)	Circ. time: Arm to leg (sec.)	Total cholesterol (mg. per 100 cc.)	Total plasma protein (%)	Body weight (lbs.)	ECG	Remarks	Capillary permeability
1	J. C.	49	1/15/43	−39	24	43	260	7.38	139	P–R prolonged low T waves in all leads, low voltage	...	+++ see Fig. 5
			1/25/43	−24	23	45	..	..	128	No change	½ gr. thyroid daily since 1/15/43	+ upper limit of normal
2	R. S.	65	4/ 2/43	−38	20	36	555	8.95	129	Low voltage, low T waves in all leads	...	+ see Fig. 5
3	R. W.	35	4/ 7/43	−44	23	61	544	7.87	139	See Fig. 8	...	+++ see Figs. 5 and 6
4	G. F.	63	2/19/43	−42	16	35	480	7.90	149	Post. wall infarct	...	++++ see Fig. 5
5	M. S.	47	12/31/42	−17	21	50	..	..	144	Somewhat low voltage	...	+++ see Fig. 5

TABLE 2.—R. W., 35 YEARS, WHITE FEMALE

Date of exam.	B.M.R.	Circ. time: Arm to lips (sec.)	Circ. time: Arm to leg (sec.)	Total cholesterol (mg. per 100 cc.)	Total plasma protein (%)	Body weight (lbs.)	Therapy (thyroid in grains)	Remarks	Capillary permeability, see Fig. 6
4/ 7/43	−44	23	61	544	7.87	139.5	...	...	+++
4/27/43	−40	22	55	..	..	138.0	¼ since 10 days	No clinical change	++
5/ 2/43	−43	20	40	340	8.16	136.5	½ since 12 days	No marked change	++
6/16/43	−26	16	24	150	..	133.0	1 since 8 days	Improv., normally menstruated for first time since 13 years	Normal
7/ 6/43	−12	17	25	140	..	129.0	2 since 7 days	Marked improv.	Normal
7/13/43	..	18	30	..	..	128.0	2	Marked improv.	Normal
7/17/43	−12	15	23	140	7.20	128.0	2	Perspires for first time	Normal
9/28/43	−15	14	28	173	6.70	125.0	2 constantly	.....	Normal

higher transparency than normal is disproven by two facts. First, the edema present in the skin tends to decrease the fluorescence since it makes the distance between skin surface and capillary loop wider. Second, direct intracutaneous dye injections into a given pre-set depth did not show any difference in fluorescence in the skin of these patients with myxedema as compared to normals.

After treatment has been instituted, the permeability curve returned rapidly to normal, although no change in the transparency of the skin was noticeable. This return of the permeability curve to normal coincided with marked loss in weight, abundant diuresis, return of the ECG and cholesterol to normal. The plasma proteins returned only later to a basic value.

The amount which diffuses in ultrafiltration through a membrane is directly proportional to the pressure.

Since it is generally agreed that in myxedema the number of capillaries per square millimeter is markedly diminished and since in our cases the diffusion of fluorescein was up to 200% of normal, one can hardly believe that an increase in intracapillary pressure could have caused this increased staining. If this were so and assuming that the number of capillaries per square millimeter were decreased by 50%, one would have to assume that the intracapillary pressure is increased 4 times normal.

This, however, is physiologically impossible.

It seems, therefore, safe to assume that the decrease in capillary permeability under thyroid therapy is the causative factor in the regress of the generalized interstitial edema and the polyserous effusions, which in turn were caused by an abnormally high capillary permeability. It may, therefore, further be assumed that this high capillary permeability is caused by lack of thyroid hormone. There is at present no evidence to indicate that the lack of thyroid hormone causes lack of some other substance which in turn directly causes the change in the capillary endothelium. Such a possibility, however, cannot be excluded. This effect of the thyroid hormone may also explain its diuretic effect in other diseases with a low metabolic rate.

One other possibility should also be mentioned here. Elmby[1] showed that in myxedema the reduction capacity as caused by a lack in ascorbic acid is markedly decreased. Since ascorbic acid has in all probability some influence on capillary permeability this possibility must be kept in mind.

The rapid return of the ECG to normal takes place at the time when the permeability curve returns to normal. This seems to indicate that in many cases, especially in younger patients, the changes are caused much more by the interstitial edema in the heart muscle than by actual changes in the coronary arteries.

Summary. 1. Myxedema tends to form serous effusions, especially in the pericardium, and also a generalized edema. There is marked interstitial edema in the heart muscle.

2. A method using the dye fluorescein is described which, by means of the Dermofluorometer, a photoelectric skin colorimeter, permits the exact estimation of capillary permeability.

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3. The values found with this method are in a narrow range for normal individuals (20 cases).

4. Cardiac edema and edema of the lower extremities in cirrhosis of the liver do not go along with an increased capillary permeability, while edema due to undernutrition and severe avitaminosis shows a marked increase in capillary permeability.

5. Five cases of myxedema all showed a marked increase in capillary permeability.

6. With thyroid therapy the permeability rapidly returns to normal, simultaneously with a marked diuresis.

7. The changes in the electrocardiogram before and after treatment are partly attributed to this change in capillary permeability.

8. All cases of myxedema had a prolonged circulation time which returns to normal with effective treatment.

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FACTORS INFLUENCING THE RETURN OF TOLERANCE FOR GLUCOSE IN MIDDLE-AGED OBESE DIABETICS*†

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In recent years there has been renewed emphasis on the mildness of the obese cases of diabetes in contrast to the inherent severity of the

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thin cases. Fetter, Durkin and Duncan[5] in this country and Schmidt[12] in Europe have been active exponents of this classification of diabetic patients. Draper,[2] combining anthropologic and clinical studies of a large group of patients with diabetes mellitus, reported an 88% correlation of the mild status of obese "pituitary" cases, and the severity of the thin "pancreatic" type. Kepler[8] has found a relationship between the response of patients to protamine zinc insulin therapy and clinical grouping based on the age and weight of patients. He found that the obese adult diabetic is relatively easily controlled with small doses of protamine zinc insulin. Newburgh and Conn[10] have reported many obese patients with hyperglycemia and glycosuria who had a complete return of their carbohydrate tolerance following a reduction in their weight.

The conclusions of a statistical study in this clinic[7] pointed out that a consideration of diabetic patients, whose diabetes manifested itself after the age of 40 years and who were obese at the onset, must follow a kinetic rather than a static viewpoint. The response of a diabetic to treatment at the onset of his illness gives only a snap-shot of an episode, while the disease goes on for many years. Several factors that alter the course of the disease were pointed out; these factors change the clinical picture so that varying degrees of severity eventually occur in patients with originally mild diabetes. Further studies of these factors form the purpose of this report.

Methods and Results. Fifty-five ambulatory diabetics were selected at random in the Diabetic Clinic of the Long Island College Hospital. All these patients were markedly obese and over the age of 40 years at the *onset* of their diabetes. Patients whose diabetes was of long duration and who were not seen by a member of the clinic at the onset of the disease were instructed to bring old photographs to substantiate their obesity. Old hospital records were found for many of the long-standing cases yielding data concerning the nature of the onset of the diabetes in some patients 10 to 15 years before this study.

All obese patients were initially put on low-caloric diets until the glycosuria was absent and the patients lost weight. Small additions of carbohydrate-containing foods were later made when the patient's condition improved until the carbohydrate content of the diet was above 180 gm. Patients who were obese at the onset but had lost weight before the time of this study, were usually given diets containing C50, P75, F60. In all cases it was attempted to render the urine free of sugar and to bring the fasting blood sugar to normal levels.

The final estimation of the ability of a patient to regain tolerance for carbohydrate was made, bearing Wilder's cautions[13] in mind. In this series, no patient had complications known to aggravate the derangement of carbohydrates metabolism, such as infections, liver disease, hyperthyroidism, pregnancy, acromegaly, etc. Since remarkable increases in the glucose tolerance of patients under treatment may come as long as 1 year after therapy is started, the case records of the patients herein reported were rechecked 4 years after the original study. In no case was the first estimation of tolerance found to be wrong.

A modification of the 2-dose oral glucose tolerance test of Exton and Rose[4] was employed. Twenty-five grams of dextrose instead of the usual 50 gm. were given in each dose since all of the patients were known diabetics. Glucose tolerance tests that proved to be normal were repeated (1 exception) with two 50-gm. doses. Capillary blood sugars were estimated by the method of Hagedorn and Jensen[6] with double determinations.

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Glucose tolerance tests were done at varying intervals on each patient. Only the final test is given in this report. The blood sugar after the second dose is considered the best criterion of poor response to glucose, as also recommended by the Mayo group. Only the first obtainable urine reports and fasting blood sugars are given, since the first glucose tolerance tests in some patients were done after treatment was started.

TABLE 1.—PATIENTS WITH DIABETES OF RELATIVELY RECENT ONSET (ALL PATIENTS OBESE AND OVER AGE OF 40 YEARS AT ONSET)

		Before treatment fasting glucose		Exton-Rose test* blood glucose						
	Sex	Blood (mg. per 100 cc.)	Urine	Fast. (mg. per 100 cc.)	1st ½ hr. (mg. per 100 cc.)	2nd ½ hr. (mg. per 100 cc.)	CHO of diet (gm.)	Loss in weight (lb.)	Duration of diabetes	Insulin P.Z. (units)
Group A. Patients Losing Weight During Treatment (14 Patients)										
M.N.	F	300	++	116	139	157	230	70	R	
F.S.	F	175	+	99	124	143	208	21	R	
W.L.	M	124	++	117	147	154	220	15	R	
M.B.	M	215	++++	92	140	151	200	25+	R	
M.M.	F	224	++	107	153	167	202	23	R	
N.R.	M	130	++	97	132	157	207	21	R	
M.K.	F	207	++++	85	118	124	200	38	1 yr.	
R.H.	F	231	++++	116	194	218	200	24	1 yr.	
A.S.	M	221	++++	121	149	187	167	30+	1 mo.	
M.D.	F	315	+++	105	150	196	200	?	R	
W.	M	172	++	113	145	192	180	38	9 mos.	
M.R.	F	180	+++	129	204	247	180	15	1 mo.	
R.S.	F	350	++++	108	148	179	175	31	1 yr.	
P.D.	M	325	++++	112	162	198	200	28	R	
Group B. Patients Who Lost Weight Before Treatment Was Instituted (13)										
A.H.	F	?	++++	125	143	218	150	60	5 yrs.	
F.R.	F	293	++++	114	167	232	110	27	6 mos.	
J.S.	F	300	++++	122	188	237	150	38	7 mos.	
E.M.	F	?	++++	110	177	222	160	32	3 mos.	
M.T.	F	311	++++	132	215	253	210	36	2 mos.	
A.C.	M	404	++++	160	191	237	165	36	1 mo.	
E.S.	F	386	++++	131	222	247	165	37	3 yrs.	
J.C.	M	401	++++	177	231	263	100−	22	4 yrs.	
M.R.	M	265	++++	120	158	210	180	95	6 mos.	
M.Y.	F	?	++++	119	132	210	220	20	9 mos.	10
J.V.	M	182	++++	96	131	181	210	41	1 yr.	14
C.M.	F	?	++++	134	201	264	213	32	2 yrs.	13
A.P.	F	237	++++	123	182	253	190	33	2 mos.	20
Group C. Patients Who Restricted CHO But Did Not Lose Weight (8 Patients)										
M.B.	F	?	++++	130	187	253	175	5	2 yrs.	
M.R.	M	?	++++	132	170	234	200	0	5 yrs.	
F.U.	F	163	++++	147	159	177	170	0	3 yrs.	
B.B.	M	275	++++	140	155	228	60	0	1 yr.	
F.M.	M	255	++++	152	223	297	150	8	R	
J.B.	F	?	++++	150	184	228	165	5	R	
A.C.	M	300	++++	150	224	259	150	0	R	
F.C.	M	294	++++	178	223	248	100	15	R	

R represents diabetes recently discovered.
* Modified; see text.

The tables given below summarize the results of the study. Table 1 includes patients who were obese and whose hyperglycemia and glycosuria were of relatively recent onset. The sub-groups are divided according to whether they had lost weight or not and also as to whether the loss in weight was due to treatment or neglect. Table 2 includes patients who also were overweight at the onset and who also were older than 40 years; however, the present study of these patients was made a long time after the diabetes was first found. Table 3 tabulates the patients who did not coöperate and who did not adhere to the prescribed diets.

The results will be discussed in light of 4 factors: (1) the weight loss factor; (2) the length of time between the onset of the illness and treatment; (3) the coöperation of the patient; (4) the age of the patient.

The Weight Loss Factor. Newburgh and Conn[10] studied obese middle-age patients who had previously been classified as true diabetics

because of hyperglycemia and glycosuria. When the weights of these patients were reduced by dieting to an ideal level, it was found that glucose tolerance tests became normal. The work of these authors would lead to the belief that most of the obese middle-aged patients who have glycosuria and hyperglycemia fall into this class. In our series of 55 cases, 14 patients (Group A) were all abnormally obese and were older than 40 years. The glycosuria and hyperglycemia had been discovered recently; they all coöperated fairly well in dieting. Only 7 of these patients had normal glucose tolerance tests after varying periods of time, while 7 did not, despite a reduction of their weight to ideal levels.

TABLE 2.—PATIENTS WITH DIABETES OF LONG DURATION (PAST HISTORY REVEALING THAT THEY WERE OBESE AND OVER AGE OF 40 YEARS AT ONSET)

		Before treatment fasting glucose		Exton-Rose test* blood glucose						
	Sex	Blood (mg. per 100 cc.)	Urine	Fast. (mg. per 100 cc.)	1st ½ hr. (mg. per 100 cc.)	2nd ½ hr. (mg. per 100 cc.)	CHO of diet (gm.)	Loss in weight (lb.)	Duration of diabetes	Insulin P.Z. (units)
Group D. Patients Remaining Obese for Many Years But Recently Attempting Diabetic Control (7 Patients)										
S.P.	F	392	++++	187	238	217	145	0	8 yrs.	30–0–0
L.M.	F	244	++++	244	316	326	160	?	7 yrs.	0
P.S.	F	?	++++	270	318	448	180	23	8 yrs.	0
S.B.	F	346	++++	232	328	400	60	11	7 yrs.	0
M.C.	F	246	++++	192	224	311	125	5	15 yrs.	15–0–15
R.I.	F	?	++++	190	259	281	110	10	13 yrs.	0
J.A.	F	?	++++	175	221	269	125	0	8 yrs.	25–10–10
Group E. Patients Who Are Thin and Now Attempting Diabetic Control (5 Patients)										
E.H.	F	?	++++	116	128	143	150	36	10 yrs.	5–5–5
A.M.	F	?	++++	132	148	184	150	21	5 yrs.	10–0–10
A.G.	F	?	++++	151	182	267	150	40	10 yrs.	10–0–10
A.K.	F	?	++++	166	195	200	150	50+	13 yrs.	15–15–15
K.J.	F	?	++++	143	200	267	180	92	12 yrs.	10–0–10

* Modified; see text.

Thirteen other patients of the same age group (Group B) gave the history of having been excessively obese relatively recently, but had lost considerable amounts of weight in spite of continued eating before coming to the clinic. Most of these patients did not know they had glycosuria before being examined. Limitation of their food consumption to a low-caloric level was followed by marked improvement of the total carbohydrate tolerance as manifested by the fact that larger diets could be subsequently given with the urines remaining sugar free and the fasting blood sugar returning to a normal level. Despite the previous loss in weight which in many cases was greater than in Group A, none of these patients demonstrated a normal glucose tolerance test after repeated follow-up studies. Even those cases treated with protamine zinc insulin did not have normal glucose tolerance tests after they had become "sugar free."

Group C in Table 1 includes patients similar to those reported by Newburgh and Conn.[10] These patients were indistinguishable from those in Group A as far as history and physical characteristics are concerned. However, they only restricted their carbohydrate intake but did *not* diminish the total food consumption sufficiently to insure loss of weight. Although the urines of these patients were rapidly

cleared of glucose, the fasting blood sugars never remained at a normal level and the postglucose blood sugars rose excessively. As Newburgh pointed out, one could expect many of these patients to have a complete return of their tolerance for carbohydrate if there had been a reduction of weight.

The different results in these 3 groups of patients demonstrate that loss in weight is an important factor in the obese middle-aged people whose glycosuria and hyperglycemia is of recent onset. It is, however, not the sole factor to be considered, since the manner in which the weight is lost is important. *Dietary restriction* causing weight loss was followed by a remarkable improvement in both clinical responses to treatment as well as laboratory evidence, whereas unlimited eating led to weight loss which was followed by a permanent diminution in glucose tolerance.

It is possible that this difference may be due to the existence of 2 types of obese middle-aged patients with glycosuria and hyperglycemia, one type gaining weight as they overeat, and another group losing weight following excessive indulgence in food. If this be so, there seems to be no way to make a clinical differentiation at the time when both are overweight.

The Length of Time Between Onset and Treatment. In a previous report,[7] we attempted to point out the differences between adult patients with diabetes of recent onset and those of long duration. The rapid recovery of the ability to assimilate carbohydrate, found in properly treated obese patients whose diabetes was of relatively recent onset, stood out in contrast to the response of obese patients with long-standing diabetes. On the latter there seemed to be a fixation at a low level of the power to assimilate carbohydrates. To illustrate this, the response of 4 obese patients, 2 of recent onset and 2 of long duration, is included. The modified 2-dose glucose tolerance tests are given as well as the carbohydrate content of the diets at the time the tests were made.

Case Studies. CASE 1. *Recent Onset.* L., age 52, male, sales clerk, markedly obese. Glycosuria was discovered during a routine examination 1 week before treatment was started. At the time, the fasting blood sugar was 164 mg. per 100 cc. but no glucose tolerance test had been done.

Length of treatment	Diet	Blood sugars (mg. per 100 cc.)			Urine	
		Fast.	1st ½ hr.	2nd ½ hr.	Fast.	1 hr.
Onset	Unlimited	164	..	..	++++	
7 days	C60 for 1 wk.	124	181	243	0	++++
26 days	C220 for 2 wks.	117	147	154	0	0

Total weight lost during this time was 15 pounds.

CASE 2. *Recent Onset.* M.K., age 49, colored housewife, very obese at onset.

Length of treatment	Diet	Blood sugars (mg. per 100 cc.)			Urine	
		Fast.	1st ½ hr.	2nd ½ hr.	Fast.	1 hr.
Onset	Unlimited	207	287	326	++++	++++
56 days	C180 for 2 wks.	149	203	287	0	++
7 months	C200 for 2 wks.	85	118	124	0	

Total weight lost was 38 pounds.

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The recovery of the ability to utilize carbohydrates in these patients was shown by: (1) complete disappearance of the glycosuria; (2) the continued absence of glycosuria despite additions of carbohydrate to the diet; (3) the tendency for the fasting blood sugars to continue to fall to normal; and (4) the glucose tolerance tests approaching the normal standards. In most cases the glycosuria disappeared by the 1st or 2nd week and the fasting blood sugar was decidedly lower by this time although it did not always return to normal level until several months had elapsed. In this same length of time, many obese cases with long-standing diabetes showed none of these characteristics. In fact, many times the urinary sugar and blood sugar *increased* when on restricted diets, as in the next 2 cases.

CASE 3. *Diabetes of 13 Years Duration (plus).* R., age 54, housewife. The patient had been followed in the clinic for 13 years. Her old records showed that by dieting she could readily clear up her glycosuria, however, she was a "chronic cheater" and remained obese. She had refused insulin for all these years despite continued glycosuria. The present study was performed when she was hospitalized for study of a recent precordial pain and for dietary regulation. In the hospital, hypertensive heart disease was found; the EKG was normal. A diet containing 1130 calories was given for 3 weeks while she was studied; no insulin was used. "Traces" of sugar were usually present in her urine. The fasting blood sugars tended to rise and more sugar appeared in the urine during this time despite a loss of weight. The following tests were performed while the patient was in the hospital; the tests which were performed while she was treated in the clinic are not included because of the probability that she did not rigidly adhere to her diet.

Length of treatment	Diet	Blood sugars (mg. per 100 cc.) Fast.	1st ½ hr.	2nd ½ hr.	Urine Fast
Onset	C135 P60 F65	160	215	263	++
18 days	C110 P60 F50	192	259	281	+++

Total loss of 11 pounds in 18 days.

The study was discontinued so that insulin could be started. She subsequently received insulin 20–10–10 to regulate the diabetes.

CASE 4. *Diabetes of 10 Years Duration (plus).* J., age 55, housewife. This patient was a known diabetic for 7 years. She remained obese, eating large quantities of candy, cake, etc., and did not pay attention to the pruritis, polydipsia, etc. She entered the hospital because of a severe neuropathy. In the hospital she was kept on a 900-calorie diet for over a week. During this time, the urine continued to give a brick red "Benedict's" reduction and the fasting blood sugars rose from 314 to 322 mg. per 100 cc. despite a loss of 4 pounds in weight.

Length of treatment	Diet	Insulin	Blood sugars (mg. per 100 cc.) Fast.	1st ½ hr.	2nd ½ hr.	Urine Fast.
Onset	"Restricted"	None	314	N.D.	N.D.	++++
9 days	C60–900 cal.	None	322	340	354	++++
7 days more	C125–1400 cal.	30 P.Z.I.	266	309	341	++++
4 days more	C125–1400 cal.	45 P.Z.I.	202	231	326	++++
2 months	C125–1400 cal.	25–10–10	175	221	269	+

There was a total loss of 17 pounds during this period.

In this series of 55 obese diabetics, there were 7 patients (Group D in Table 2) who had remained markedly obese during many years because

of neglected treatment. Some had been given "free diets" with "insulin to cover." All of these patients were persuaded to attempt diabetic control with low-caloric diets; none of these patients demonstrated an ability to regain carbohydrate tolerance after losing weight. Four of these 7 patients were hospitalized; the course in the hospital corroborated the experience in the clinic. The 2-dose glucose tolerance tests after they had been on low-caloric diets were uniformly bad. The fasting blood sugar values were always higher than normal, and the postglucose responses were markedly exaggerated. To 5 of these 7 patients, the inability to reduce the glycosuria with diet alone came as a surprise, since they had been able to do so in the past. Such histories suggested that the persistent and long-standing neglect in restricting the caloric intake led to a progression in the severity of the diabetes ending in a permanent depression of the glucose tolerance.

The fact that both the length of time a patient has had improper treatment as well as the lack of adequate weight reduction seem to impair the ability of middle-aged obese diabetics to regain tolerance for carbohydrate raises the question as to which of the two is more important. In the diabetic clinic we have followed many patients similar to those in Group A in whom there has been no return of glycosuria or hyperglycemia after 8 years; this coincides with Newburgh's findings. However, a study of the 5 patients in Group E (Table 2) was informative. These patients had been markedly obese at the onset of their diabetes many years before the present study. Most of them gave a typical history of having followed a restricted dietary regimen for variable periods of time after the diagnosis had been made. However, after they had lost weight they became more careless in dieting, leading to a return of a severe diabetic state. For the most part, low-caloric diets given during the present study decreased the glycosuria and lowered the fasting blood sugar. Insulin had to be given early in the course of treatment because of obvious difficulty in keeping such patients on low-caloric regimen. A comparison of the end-results of treatment of these "thin patients with long-standing diabetes" (Group E) with "thin patients with diabetes of recent onset" (Group B) is interesting. All of the former had a definitely lowered tolerance for carbohydrate than the latter, as evidenced by the fact that all of the former needed insulin and the diets could not be raised to as high levels without a return of glycosuria. It was interesting to note, however, that the 2-dose glucose tolerance tests (which were performed after unmodified insulin had been given on the previous day) were of "moderate severe degree" in contrast to the tests obtained in "obese patients with long-standing diabetes (Group D) which were exceedingly bad." These findings suggest that prolonged neglect in the treatment of the mild adult form of diabetes leads, after a period of time, to a restriction in the amount of carbohydrate that the patient can consume, but that the patient's ability to manage glucose efficiently is not as markedly impaired by this factor as it is by lack of an adequate reduction in weight.

It must be pointed out that most of the patients reported here as

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having "long-standing diabetes" had the diagnosis originally made over 7 years before the present study. Because of the small number of cases reported here, an adequate estimation of the length of time that it takes for the diabetes to progress cannot be made.

The Coöperation of the Patient. In a recent study, Colwell[1] claimed that diabetes mellitus became progressively more severe in all patients, and that the rate of progression was more or less determined at birth. He found in his large series of patients that treatment altered the natural course of the disease for only a few years, after which the progressiveness again manifested itself. This is in contrast to the views of many older clinicians, such as Naunyn, who found that diabetes could be checked by dietary management. In this study, it was obvious that coöperation on the part of a patient in following dietary prescriptions was a very important factor in the eventual results. For instance, when separating the patients in Group A from those in Group C, the chief criteria were that the former coöperated strictly and lost weight, whereas the patients in the latter group restricted their food intake sufficiently to become aglycosuric, but not to the extent that they could lose weight. Differences in coöperation are stressed when non-diabetic obese patients are studied, but are not emphasized in diabetic literature. However, the extreme importance of this factor in diabetics was shown by the fact that careful adherence to the low-caloric regimen by patients in Group A was rewarded by a return to normal carbohydrate tolerance in at least 50% of the cases, and by the fact that none had glycosuria after the oral administration of 50 to 100 gm. of glucose. Patients in Group C did not show such excellent results. Their fasting blood sugars remained elevated and although the postabsorptive urine contained no glucose, most had glycosuria after the administration of two 25-gm. doses of glucose.

TABLE 3.—PATIENTS WHO ARE OBESE AND OVER AGE OF 40 YEARS (NOT COÖPERATING WITH DIETING)

		Before treatment fasting glucose		Exton-Rose test[1]* blood glucose						
	Sex	Blood (mg. per 100 cc.)	Urine	Fast. (mg. per 100 cc.)	1st ½ hr. (mg. per 100 cc.)	2nd ½ hr. (mg. per 100 cc.)	CHO of diet (gm.)	Loss in weight (lb.)	Duration of diabetes	Insulin P.Z. (units)
		Group F.	*Cases Similar to Group A (3 Patients)*							
G.P.	F	320	++++	222	287	324	60?	14†	1 yr.	0
B.F.	F	254	++++	219	281	336	200?	19†	½ yr.	0
R.N.	M	?	++++	150	255	353	215	0	½ yr.	40–0–0
		Group G.	*Cases Similar to Group E (5 Patients)*							
A.C.	F	?	++++	170	206	250	165	30	14 yrs.	20–0–0
M.M.	F	325	++++	204	242	285	180	50	11 yrs.	22–0–0
F.M.	F	320	++++	197	262	300	150	40	12 yrs.	0
I.N.	F	?	++++	286	298	348	180	40	7 yrs.	15–0–10
C.M.	F	122	++	221	314	385	170	58	9 yrs.	0

* Modified; see text.
† Gain of weight.

The differences in the results just mentioned were due to relatively minor infringements in dieting. An additional 8 patients did not restrict their food intake at all. Three of these (Group F, Table 3) should have had results similar to Group A or Group C since they were also obese, over the age of 40 years at onset and the diabetes was dis-

covered shortly before this study. However, because of constant misbehavior they had very high fasting and postglucose blood sugars. All 3 were subsequently given protamine zinc insulin, which did not clear up the glycosuria. Similar results were found by Fetter, Durkin and Duncan[5] who pointed out that obese diabetics cannot be controlled by insulin alone when they do not restrict their diets at all. The patients later become the "obese cases with long-standing diabetes" who after 6 or 7 years do not have a return of carbohydrate tolerance even when dieting strictly.

Another interesting contrast was presented by the 5 patients in Group G in Table 3. These patients had lost tremendous amounts of weight because of lack of proper dieting over many years. The fact that their weight had been reduced to normal or below did not alter the necessity for dieting. The high-fasting and postglucose blood sugars were reflections of the patient's lack of adherence to a proper diet. It is our impression that these patients with diabetes neglected over many years feel better when their blood sugars are allowed to remain at a higher level; we do not attempt to obtain rigid chemical control in the clinical management of such patients. For this reason, it is emphasized that the results found in Group G are included merely for comparison with those obtained in Group E, since both had similar clinical backgrounds, but they differed in the degree of coöperation in dieting.

The Age Factor. Statistical studies have shown that incidence of obesity becomes the most important factor in the etiology of diabetes at the period of life that may be called "the beginning of middle age." As was demonstrated above, the presence of obesity is the most important factor influencing the progression of the disease. However, the age factor cannot be overlooked. Colwell's[1] studies show that the rate of progression of diabetes is slower when the disease manifests itself clinically at a later age. Thus the earlier the age of onset, the severer is the future course of the diabetes. In this clinic, the onset of the diabetes at 40 years of age is selected as the dividing line between so called "middle-aged obese" and young diabetics. Others have chosen 35 years to 45 years as the dividing age of onset. One of the chief criticisms leveled against the grouping of diabetics according to age and weight is that there are too many exceptions when any one single age level is chosen. Against these objections are the many advantages of making these groupings so that early diagnosis, definitive treatment, and specific aims in therapy can be emphasized as has been done above. The age of onset was selected as 40 years because we have seen many obese patients between the age of 35 years and 40 years (particularly women whose diabetes was found during pregnancy) whose deranged carbohydrate metabolism rapidly became worse even with treatment within a period of 3 to 5 years. In contrast, we have seen exceptionally few obese diabetics whose disease seemed to manifest itself after the age of 40 years who have not had a mild subsequent course. In fact, in patients who coöperated well, the disease became milder with time.

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Conclusions. Obese patients who are over 40 years of age when they first have glycosuria and hyperglycemia should be treated by rigid dietary restriction aiming for reduction of weight, for disappearance of glycosuria, and for a physiologic blood sugar level. When treated in this manner, there may be a remarkable return of tolerance for carbohydrate. Careful coöperation in following the dietary prescription on the part of the patient is needed to obtain these results.

The diagnosis of diabetes must be made early in such patients, because if weight is lost by neglect in treatment, the ability to regain tolerance for carbohydrate becomes impaired. Response to treatment in such patients is still good, particularly when protamine zinc insulin is used.

Obese patients who neglect treatment for many years and remain obese, lose the ability to regain their tolerance. They become difficult to treat. Diet therapy in these patients seems to be of little value. Their blood sugar levels remain elevated even with insulin. Those patients who neglect treatment for many years and who eventually lose weight also show diminished tolerance, but the management of the deranged glucose economy is less difficult than in those who remained obese.

Summary. 1. Glycosuria and hyperglycemia occurring in obese patients after the age of 40 years represent a temporary decrease in the patient's tolerance for carbohydrate.

2. Prompt treatment consisting of weight reduction by means of low-caloric regimens can lead to a remarkable return of the patient's tolerance for glucose. In some cases, the deranged carbohydrate tolerance becomes normal.

3. A kinetic viewpoint must be maintained when viewing the course of these cases. The most important factors diminishing the ability of a patient to regain carbohydrate tolerance are: (*a*) the lack of proper weight reduction; (*b*) delay in treating the patient over a period of years; (*c*) poor coöperation on the part of the patient in following a dietary regimen which aims at effecting a weight loss; (*d*) the onset of the diabetes at an early age.

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THE RELATIONSHIP BETWEEN HORMONAL ABNORMALITIES AND ACCIDENTS OF LATE PREGNANCY IN DIABETIC WOMEN*

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Previously reported studies from this laboratory of hormonal changes during pregnancy[1-5,7] have been primarily concerned with toxemia and have indicated that preëclampsia and eclampsia in diabetic as in non-diabetic women are characteristically preceded and accompanied by a typical imbalance as revealed by aberrations from the normal in the measurable hormones or hormonal products of the blood and urine. An abnormal rise in the chorionic gonadotropin (C.G., A.P.L., prolan) of the serum 4 to 8 weeks prior to any clinical signs is the most easily detected of these changes, but has been a less consistent finding than urinary evidence of a changed metabolism of the placental steroids involving a progressive deficiency of estrogen and progestin and culminating in more rapid destruction of estrogen.

In our early studies of diabetic pregnancies, there was some indication that the same hormonal abnormality which typifies preëclampsia and eclampsia also pertained in those accidents of late pregnancy involving death of the offspring, a frequent occurrence in diabetic women. As a result of our findings and at our instigation, administration of estrogenic and progestational substances to diabetic patients showing an abnormal rise in serum C.G. has been given a rather extensive trial at the George F. Baker Clinic of the New England Deaconess Hospital. Articles from this laboratory[1,2,3,5] have covered our studies of 33 of the cases reported independently from that clinic.[11-14] The present investigation, conducted entirely on diabetic women to whom no hormones were administered, was undertaken primarily with the purpose of obtaining more complete data concerning the consistency of the relationship between hormonal abnormalities and the development of later clinical mishaps, particularly those involving fetal or neonatal death. We were also interested in following the metabolism of the placental steroids from an earlier period of gestation than has previously been studied except in normal pregnancy.

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Material and Methods. In 16 pregnant women with diabetes, serum C.G. was measured at 1- to 2-week intervals starting between the 16th and 29th weeks. In 8 of them, the metabolism of the placental steroids was also studied by repeated quantitative analyses of 24-hour specimens of urine for estrogen metabolites. The same methods of analysis of serum[2] and urine[5,9] were used as in previous studies except that estrone and α estradiol fractions were separated by a micro-modification of the Girard method and assayed individually rather than depending upon the difference in activity before and after treatment by semicarbazide for the estimation of estrone. Urinary pregnanediol was not measured, since previous findings indicated that the excretion of this compound runs roughly parallel to that of estriol, and gives no information about the metabolism of progestin that is not more adequately provided by determining the amount and partition of the separated urinary estrogens and the amount of additional potency that may be derived from urine by hydrogenation with zinc and HCl.

TABLE 1.—CLINICAL NOTES ON PREVIOUS PREGNANCIES AND DIABETES

Name	Age	Parity	Date of this pregnancy	History of previous pregnancies	Diabetes first diagnosed*	Daily insulin requirements
Cases With Abnormal Elevation of Serum Chorionic Gonadotropin						
R. S.	23	II	1942–43	1 stillborn 1939	Fol. 1st dely. 1939	72 U. Prot. Zn 25 U. reg.
E. C.	38	III	1941–42	2 stillborns 1930, 1931	1923	32 U. Prot. Zn 20 U. reg.
E. H.	30	I	1941–42	....	This preg. 26th week	12 U. Prot. Zn
J. L.	27	I	1941	....	This preg. 23rd week	None
F. L.	19	I	1940–41	....	1938	90 U. reg.
E. S.	25	I	1942–43	....	1929	35–40 U. Prot. Zn 12 U. reg.
S. L.	26	I	1941–42	....	1931	60–80 U. reg.
Cases With Normal Serum Chorionic Gonadotropin						
C. H.	25	I	1942	....	1939	80–120 U. reg.
M. M.	36	II	1942	1 stillborn 1932	1933	30–45 U. reg.
E. D.	21	II	1941	1 nor. 1939	1938	70 U. Prot. Zn 20 U. reg.
E. B.	25	II	1941	1 nor. 1939	Last preg. 1939	12–28 U. reg.
L. S.	39	X	1942	8 nor., 1 misc. 1925–1939	This preg. 1st visit†	16 U. Prot. Zn
D. H.	23	I	1942–43	....	1938	52 U. Prot. Zn 20 U. reg.
E. F.	23	I	1941–42	....	1940	52–72 U. Prot. Zn
A. P.	29	V	1940–41	4 nor. 1930–38	This preg. 28th week	None
I. S.	37	IV	1941–42	3 nor. 1924–1936	This preg. 23rd week	16–40 U. reg.

* Glycosuria with or without symptoms, a glucose tolerance curve of the diabetic type and a fasting blood sugar of 140 mg./100 cc. or over.

† Excessive thirst since 1940.

Serum Chorionic Gonadotropin and Later Accidents. Clinical data in relation to the values for serum C.G. are summarized in Tables 1 and 2, and indicate that neither the duration nor the severity of the diabetes are factors in an abnormal elevation of serum C.G. Furthermore, the incidence of toxemia and the size or condition of the offspring appear to be unrelated to the history or severity of the disease. All of the

patients were seen at weekly intervals throughout pregnancy by one of us (D.H.) for careful control of the diabetes.

TABLE 2.—CLINICAL NOTES ON THE PREGNANCIES STUDIED

	Late pregnancy toxemia*					Delivery		Condition of offspring	
Name	Alb.	Hyp.	Ed.	S.S.	Conv.	Week of gestation	Type	Weight	
Cases With Abnormal Elevation of Serum Chorionic Gonadotropin									
R. S.	−	−	−	−	−	40	Spont.	Macerated	Stillborn; died 3 wks. pre-part.
E. C.	+	−	+	−	−	34	Cesarean	6 lb. 11 oz.	Intraut. asphyxia, cyanosis, survived
E. H.	+	−	+	−	−	39	Spont.	8 lb.	Normal
J. L.	+	−	+	−	−	40	Spont.	9 lb. 4 oz.	Normal
F. L.	+	+	+	+	+	39	Induced	8 lb. 3 oz.	Normal
E. S.	+	+	+	−	−	35	Spont.	Macerated	Stillborn; died 2 wks. pre-part.
S. L.	+	+	+	+	−	35½	Induced	5 lb. 11 oz.	Died 36 hrs. post-part., left subarachnoid hemorrhage
Cases With Normal Serum Chorionic Gonadotropin									
C. H.	+	−	+	−	−	39	Induced	6 lb. 4 oz.	Normal
M. M.	+	+	+	−	−	37	Spont.	6 lb. 12 oz.	Stillborn, intraut. asphyxia; died 3 days pre-part.
E. D.	−	−	−	−	−	35	Spont.	7 lb. 8 oz.	Normal
E. B.	−	−	−	−	−	36½	Spont.	8 lb. 4 oz.	Died 15 hrs. post-part., intraut. pneumonia, adrenal hemorrhage
L. S.	−	−	−	−	−	32	Spont.	Macerated	Stillborn; died 1 wk. pre-partum
D. H.	−	−	−	−	−	44	Spont.	Macerated	Stillborn; died 6 wks. pre-partum
E. F.	−	−	−	−	−	39½	Spont.	6 lb. 14 oz.	Normal
A. P.	−	−	−	−	−	40	Spont.	11 lb. 4 oz.	Normal
I. S.	−	−	−	−	−	40	Spont.	8 lb. 14 oz.	Normal

* The abbreviations in the subheadings stand for the following: alb. = albuminuria; hyp. = hypertension; ed. = abnormal gain in weight or visible edema; S.S. = subjective symptoms; conv. = convulsions.

An Early Elevation of Serum C.G. This abnormality was detected in 7 of the 16 patients between the 25th and 33rd weeks of gestation.* Six of these developed toxemia of varying degrees of severity at 31 to 37 weeks and the 7th (R.S.) had intrauterine death at 37 weeks with no other clinical abnormality. In 3, toxic signs were mild, being limited to albuminuria and edema. One of these (E.C.) was delivered by cesarean section during the 34th week because of failure to control increasing albuminuria by conservative measures together with a history of stillbirth in each of 2 previous pregnancies. The 6 lb. 11 oz. baby was cyanotic for several days but survived. The other 2 had normal deliveries at term of rather large but perfectly healthy infants, one (E.H.'s) weighing 8 lb. and the other (J.L.'s) 9 lb. 4 oz. In both, the mild toxic signs disappeared during the last week of pregnancy following a lowering of serum C.G. to normal levels. In other words, both the hormonal and clinical abnormality appeared to be self-corrected.

Of the other 3 patients with an early elevation of serum C.G., one (F.L.) had eclampsia during the 39th week with delivery, after artificial rupture of the membranes, of a normal 8 lb. 3 oz. infant. Two had preëclamptic toxemia: one (E.S.) with a blood pressure of 150:90,

* Our criterion for normal serum C.G. is based upon the analyses of 235 serums from 67 normal pregnancies. In 39 of these, including 10 complicated by diabetes, repeated analyses were performed and in no case was an elevation above 100 r.u. per 100 cc. found between the 20th and 36th weeks.[5]

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albuminuria (3 gm. in 24 hours) and edema at 31 weeks and intrauterine death at 33 weeks; in the other (S.L.) labor was induced at 35½ weeks because of blurring of vision, hypertension (180/110) and albuminuria (7 to 8 gm. in 24 hours). The 5 lb. 11 oz. infant died 36 hours after birth.

Normal Serum C.G. Of the 9 patients in whom serum C.G. remained normal between the 25th and 36th weeks, 2 developed toxemia. In one (C.H.) toxic signs were limited to slight albuminuria (0.2 to 0.3 gm. in 24 hours) between the 30th week and term and edema of the ankles at term, when labor was induced and a normal 6 lb. 4 oz. infant delivered. The other (M.M.) had slight albuminuria (0.2 to 0.3 gm. in 24 hours), edema and hypertension (highest reading 150/82) starting at the 31st week. During the 37th week intrauterine death occurred. Two of the 9 with normal serum C.G. had pyelitis and spontaneous premature delivery at 35 and 36½ weeks, respectively. Both of the infants were large for this period of gestation, 7 lb. 8 oz. and 8 lb. 4 oz. The 35-week-old infant (E.D.'s) was healthy and survived, but the other (E.B.'s) died 15 hours after birth, the diagnosis after autopsy being intrauterine pneumonia and adrenal hemorrhage. There were 2 other fetal deaths in this group with normal serum C.G. One (L.S.) had intermittent uterine bleeding starting during the 25th week. Intrauterine death occurred during the 31st week. The other (D.H.) had a normal pregnancy up to the 38th week, when intrauterine death occurred. The other 3 cases of this group (E.F., A.P. and I.S.) had normal pregnancies throughout with full-term delivery of healthy infants weighing 6 lb. 14 oz., 11 lb. 3 oz. and 8 lb. 14 oz., respectively.

From this study, together with those previously reported,[2,4] it is safe to conclude that the finding of a rise in serum C.G. between the 25th and 35th weeks in either diabetic or non-diabetic women warrants the prediction of later trouble, although it gives no indication of the type or severity of the trouble, which may be only mild (and occasionally self-corrected) toxemia, preëclampsia, eclampsia or death of the offspring. However, from the data presented it is obvious that later mishaps may occur without any premonitory rise in serum C.G. Although a fairly consistent relationship is again demonstrated between such a rise and toxemia of varying degrees of severity, the incidence of fetal or neonatal death was no higher in this group than in those in whom no elevation occurred. Normal levels of serum C.G. from the 25th to 35th weeks in diabetic patients, therefore, provide no assurance that the rest of pregnancy will be uneventful, particularly as regards the prognosis for the fetus.

Metabolism of the Placental Steroids and Later Accidents. Although elevated serum C.G. has not, in our experience, been an absolutely consistent finding in preëclampsia and eclampsia,[2,4] none of 23 previously reported cases of this disease[4,6] in which repeated complete urinary analyses were done failed to give evidence of a typical abnormality in the metabolism of the placental steroids, despite the fact that in 6 of them serum C.G. was normal. We were particularly interested in determining whether or not death of the offspring was also more

closely related to deficiency of estrogen and progestin than to high serum C.G. levels. In 8 of the present group of 16 patients, urinary analyses were performed for the separated estrogens and for the increased potency produced by hydrogenation with zinc and HCl. The pregnancies of 4 (R.S., E.S., M.M. and D.H) terminated in death of the offspring, and that of a 5th (E.C.) in cesarean delivery at 34 weeks of a viable but cyanotic infant that barely survived. In all 5, evidence of a deficiency of placental steroids preceded the accident, although in 2 (M.M. and D.H.) repeated analyses of serum revealed normal levels of C.G. The failure to find high serum C.G. in some cases of fetal or neonatal death, therefore, does not exclude the possibility that the deranged metabolism of the placental steroids which characterizes toxemia of late pregnancy may not pertain.

It would also appear that if this deranged metabolism is in any way etiologically concerned in these accidents, it may take its toll either from the maternal or fetal organism but not necessarily from both. In 7 of the 8 patients whose urinary estrogens were studied, this abnormality was found. Two of them (R.S. and D.H.) had intrauterine death with no toxic signs. Two (J.L. and F.L.) had toxemia with normal offspring, despite the development in one (F.L.) of full-blown eclampsia at 39 weeks. In the other (J.L.), mild toxic signs disappeared during the 38th week coincident with a self-correction of the endocrine abnormality. Only 3 of the 7 with abnormal metabolism of the placental steroids had both toxemia and fetal abnormalities (E.C., E.S. and M.M.). E.F. was the only one of this group in whom the urinary findings reflected normal steroid metabolism, and she alone had both a normal pregnancy and a healthy child.

TABLE 3.—SUMMARY OF HORMONAL FINDINGS IN RELATION TO OBSTETRICAL OUTCOME

	Serum C.G.		Steroid metabolism		Obstetrical notes	
Name	Specs.	Results	Specs.	Results	Mother	Offspring
R. S.	9	High	9	Abnormal	Normal	I.U.* death
E. C.	9	High	3	Abnormal	Mild toxemia	Cyanotic but survived
E. H.	5	High-s.c.†	..	..	Mild toxemia	Normal
J. L.	7	High-s.c.†	5	Abn.-s.c.†	Mild toxemia	Normal
F. L.	6	High	4	Abnormal	Eclampsia	Normal
E. S.	11	High	10	Abnormal	Preëclampsia	I.U.* death
S. L.	9	High	..	..	Preëclampsia	N.N.‡ death
C. H.	5	Normal	..	..	Mild toxemia	Normal
M. M.	4	Normal	2	Abnormal	Preëclampsia Prem. dely.	I.U.* death
E. D.	6	Normal	..	..	Prem. dely.	Normal
E. B.	5	Normal	..	..	Prem. dely.	N.N.‡ death
L. S.	3	Normal	..	..	Prem. dely.	I.U.* death
D. H.	9	Normal	9	Abnormal	Normal	I.U.* death
E. F.	6	Normal	3	Normal	Normal	Normal
A. P.	8	Normal	..	..	Normal	Normal
I. S.	8	Normal	..	..	Normal	Normal

* I.U. = intrauterine.
† s.c. = self-corrected.
‡ N.N. = neo-natal.

Table 3 summarizes hormonal findings in relation to clinical outcome in all cases. The detailed results in 5 of the 8 whose urines were

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analyzed for metabolites of estrogen will not be reported here, since collections were not begun until after the 31st week. The results, therefore, add nothing to those already published except that fetal and neonatal death, whether or not accompanied by toxemia, appears to be closely associated with the same abnormality of the placental steroids which characterizes preëclampsia and eclampsia.

In Figures 1 and 2 are presented the most pertinent findings in the other 3 patients whose urines were analyzed, specimens having been collected from an earlier period of gestation than has before been studied in either diabetic or non-diabetic women in whom toxemia or death of the offspring occurred.

Explanation of Charts. T_o, *i. e.*, total urinary estrogen, expressed in terms of estrone equivalents (Fig. 1) represents the sum of the estrogenic activities found in the estradiol plus estrone plus estriol fractions. In general it may be said that a rise in T_o is due to an increase in all 3 fractions but is accompanied by a change in the partition of the estrogenic activity between these fractions which points to an increased rate of conversion of estradiol to estrone to estriol and hence to greater secretion of progestin, whose presence facilitates this conversion. Conversely, a drop in T_o is characteristically associated with a changed partition of the total activity between the 3 fractions which indicates decreased conversion of the estrogens and hence withdrawal or deficiency of progestin.*

The amount of estrogenic activity produced by Zn-HCl hydrolysis of the urine, over and above that accounted for by estrogens excreted as such, is termed "unaccounted for" T_o. The exact derivation of this activity remains to be established, although the weight of evidence points to non-estrogenic excretory products resulting from oxidation of estrogens *in vivo*. Its 24-hour value, as related to that of total estrogens excreted as such ("unaccounted for" T_{zn} to T_o ratio—Figure 2), is interpreted as providing a gauge of the rate of destruction of estrogens in the body and consequently of secretion of progestin, since progestin reduces destruction of estrogens in addition to facilitating their conversion.*

The heavy solid lines in Figures 1 and 2 are composite curves based on published data from normal pregnancies.[4,10] The double line represents the findings in one of the normal pregnancies in which repeated complete urinary analyses were started earlier than in the rest, namely, at 16 weeks. Separated estrogens in this case have been published.[3]

The 3 patients chosen for this study (R.S., E.S. and D.H.) were young, with fairly severe diabetes of 3 to 13 years' duration (see Table 1). In all, pregnancy terminated in intrauterine death, 2 with (R.S. and E.S.) and 1 without (D.H.) a preceding rise in serum C.G. E.S., the only one in whom there were any toxic signs, was placed under hospital care for preëclampsia at 31 weeks. Two weeks later the fetal heart could not be heard and a macerated fetus was delivered during the 35th week. In the other 2 patients intrauterine death occurred, without any other clinical signs of abnormality, at the end of the 37th week. Stillbirth came 3 and 6 weeks later.

The results of only the first urinalysis after death of the fetus are included in the charts. In each case this specimen was collected within a few days of the accident. Thereafter the excretion of estrogens dropped precipitously, but, even in D.H., who carried the dead pregnancy for 6 weeks, never reached non-pregnant levels until after delivery of the macerated fetus and placenta.

* For a more complete explanation of these interpretations of our findings, the reader is referred to previous publications from this laboratory.[1,2–6,8,10]

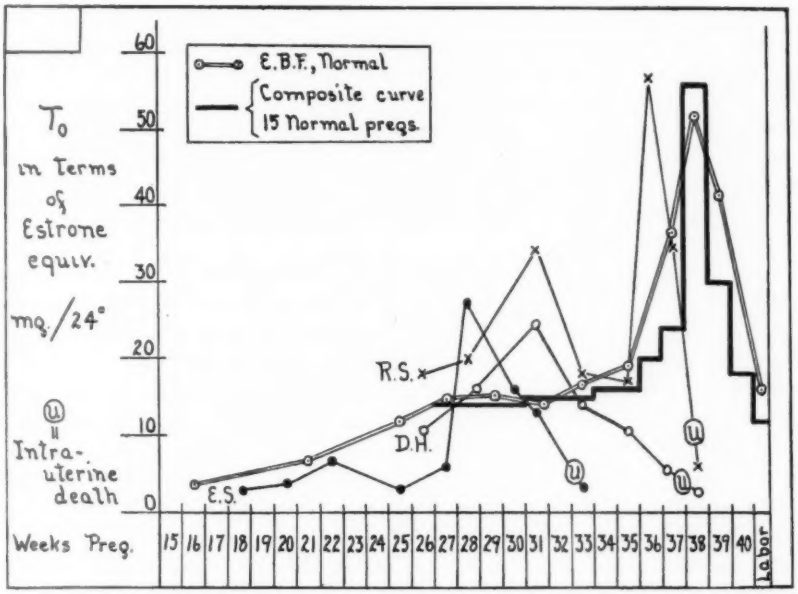

FIG. 1.—Rate of estrogen excretion. Total estrogenic activity (T_O = estradiol + estrone + estriol) of repeated specimens of urine from 3 pregnant women prior to intrauterine death compared with normal curves of total excretion of estrogens.

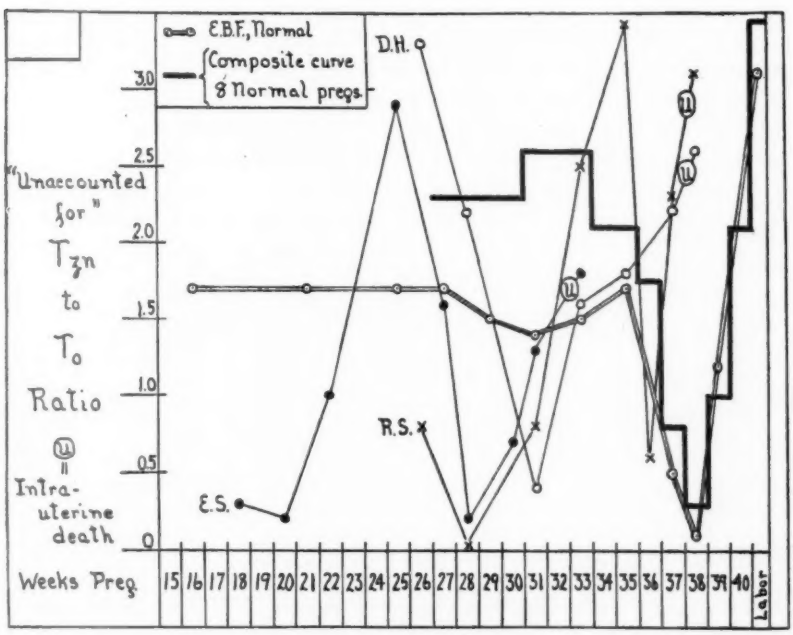

FIG. 2.—Rate of estrogen degradation. Ratio of increased activity produced by hydrogenation ("unaccounted for" T_{zn}) to total excretion of active estrogens in repeated specimens of urine from 3 pregnant women prior to intrauterine death compared with ratios based on normal pregnancies.

In each case, intrauterine death occurred at a time when the urinalyses reflected a markedly downward trend in the rate of conversion of estrogen together with a striking increase in its rate of destruction; in other words, according to our interpretation, a progressive deficiency of both estrogen and progestin. Evidence for this shift in steroid metabolism has been a consistent finding before and during the development of preëclampsia and eclampsia. It is entirely similar to the hormonal situation which immediately precedes normal labor and delivery.

In these 3 patients, moreover, all of whom were followed 12 to 15 weeks before intrauterine death, an even earlier deviation from the normal was discovered. In each, between the 25th and 31st weeks, a sudden increase in the rate of conversion (as indicated by increased excretion of all 3 estrogens, particularly estrone and estriol) and decrease in the rate of destruction (as indicated by a striking drop in the amount "unaccounted for" T_{zn}) were observed. This situation, presumably reflecting increased placental secretion of both estrogen and progestin, does not begin to develop to such a marked extent in normal pregnancy until around the 36th week. In fact, in none of the normal controls did the ratio of "unaccounted for" T_{zn} to T_o activity fall below one prior to the 35th week. In other words, the analogy between the hormonal changes which precede the development of accidents of late pregnancy and those which precede labor started earlier than has before been demonstrated and included evidence for the markedly increased rate of production and metabolic conversion of the placental steroids, which normally reaches a peak 2 to 3 weeks before labor, as well as the subsequent withdrawal phenomenon. The whole picture, therefore, indicates premature changes in the placenta with the development of toxemia or damage to the fetus or both at the time when premature labor and delivery might be expected.

In D.H., only one such period of maximum conversion and minimum destruction of the estrogens was detected, at 31 weeks; this being followed by urinary evidence of a progressive drop in the rate of conversion and rise in the rate of destruction for 6 weeks prior to fetal death. In R.S., the same pattern was followed through the 35th week. During the 36th week, however, a striking increase in total excretion of estrogen together with a precipitous drop in "unaccounted for" T_{zn} activity pointed to a spurt in the production of the placental steroids. It is interesting that the fetus was thought to be growing more rapidly and to be more active during this time. This episode, which suggests an attempt at self-correction of the hormonal abnormality, was followed by a sudden change in the opposite direction and death of the offspring. In E.S. also 2 cycles of excretion were detected. Although total estrogens were not high between the 18th and 22nd weeks, their partition and the very low values for "unaccounted for" T_{zn} indicated an unusually rapid rate of conversion of estradiol to estrone to estriol together with very little breakdown of estrogen. A high ratio of progestin to estrogen for this period of gestation is suggested. This situation was followed by evidence for a period of progestin withdrawal which was interrupted by a temporary increase in total estrogen and decrease in "unaccounted for" T_{zn} at 28 weeks. During the following 5 weeks, when the urinalyses reflected a progressive deficiency of both estrogen and progestin, toxic signs, which had previously been limited to slight albuminuria, became sufficiently alarming to render it advisable to place the patient under hospital care at 31 weeks. Two weeks later fetal death occurred.

Discussion. The finding of urinary evidence of disturbed placental metabolism starting as early as the 18th to 28th weeks in these 3 patients intimates that the primary cause or causes of the accidents of late pregnancy discussed in this paper are operative earlier than we have been led to assume from our studies of serum chorionic gonadotropin. In one of these (D.H.), values for serum C.G. were normal throughout the period of study. However, in the other 2, the first in whom urinalyses have been performed prior to any elevation of serum C.G., this elevation did not appear until at least 5 weeks after a disturbed metabolism of the estrogens was detected. The inference is that a rise in serum C.G., when it occurs, is secondary to a changed metabolism of the placental steroids. In E.S. and R.S. it was first found at 25 and 33 weeks, respectively, coincident with the first urinary evidence of estrogen and progestin withdrawal. We are thus brought back to one of our original concepts,[2] that increase of gonadotropic substance may be a compensatory measure, an attempt to counteract a failing production of estrogen and progestin. It is perhaps significant that the urinalyses on both E.S. and R.S. suggested an attempted self-correction of the steroid deficiency following the rise in serum C.G., whereas those on D.H., in whom no elevation occurred, gave evidence of uninterrupted withdrawal of estrogen and progestin over a 6-week interval prior to intrauterine death. It is conceivable that a failure to find any increase in the level of chorionic gonadotropin reflects a deficiency in the cells secreting this hormone, whereas continued withdrawal of the placental steroids despite a rise in serum C.G., which has been the usual finding in toxemic patients, may reflect a deficiency in the placental secretion of estrogen and progestin. Either of these situations would be readily accountable to damage of the placenta with resultant premature senility.

Since deficiency of estrogen and progestin is the immediate precursor of the clinical mishaps discussed in this paper, administration of these hormones during the period when such accidents are likely to occur is still a logical therapeutic approach. It would appear, however, that therapy should not be limited to patients in whom an abnormal elevation of serum C.G. is detected, since such a rise dose not develop in all patients with deranged metabolism of the placental steroids and is perhaps a secondary phenomenon. According to the data presented, one would expect almost as many fetal or neonatal deaths in cases whose serum C.G. was normal as in those with an abnormal elevation. A changed metabolism of the estrogens may be detected only by methods of urine analysis that are too laborious and time-consuming to be of clinical applicability. Although composite findings reveal that excretion of pregnanediol is low in patients in whom accidents of late pregnancy develop,[4] analyses for this urinary constituent alone is of limited diagnostic significance, since normal values vary over such a wide range.[4,10] Studies of hormones, therefore, would appear to be of little assistance in determining which patients to treat. Since the number of diabetic pregnancies seen in a year in any clinic is relatively small, and since improvements in care are sure to develop and influence

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both maternal morbidity and fetal mortality, it seems to us that conclusions concerning the effect of administering hormones may be acquired only by treating alternate patients until a sufficient number of treated cases with consecutive untreated controls has been collected to be statistically significant.

The intimation that placental abnormalities are operative prior to the period of estrogen and progestin withdrawal suggests that truly preventive measures should be started even sooner, as early as the 18th to 25th weeks. Our previous studies have led to the hypothesis that products of the oxidative inactivation of estrogens in the body play an important rôle in the mechanism which controls the production of the ovarian and placental steroids. The withdrawal of progestin before normal labor[10] and the regression of the corpus luteum prior to normal menstruation[6] have thus been ascribed to a deficiency of breakdown products of estrogen accountable to a preceding period of maximal secretion of progestin and hence of reduced destruction of estrogen. The present investigation supplies our first evidence that a similar period of increased conversion and decreased destruction of the estrogens precedes the withdrawal phenomenon associated with the onset of the clinical disasters discussed in this paper. A constant supply of breakdown products of estrogen during this period of maximal conversion, such as might theoretically be provided by the daily administration of larger amounts of estrogenic material than could be metabolized in relation to the available progestin, might conceivably prolong the period of increased secretion of the placental steroids and forestall their premature withdrawal until the maternal and fetal organisms are ready for delivery.

Summary and Conclusions. Hormonal changes during pregnancy have been studied in 16 diabetic women starting between the 16th and 29th weeks. Only 8 had normal offspring, and in all but 3 some accident of late pregnancy occurred. Chorionic gonadotropin (C.G., prolan, A.P.L.) was measured in repeated specimens of serum from all 16 patients. In 8 of them, only one of whom had a normal pregnancy, the metabolism of the placental steroids was also followed by repeated urinalyses for metabolites of estrogen.

The results indicate that an abnormal rise in serum C.G. does not always precede the accidents of late pregnancy which so frequently occur in diabetic women, particularly those involving death of the offspring. Premature withdrawal of estrogen and progestin, however, such as normally develops only during the last 2 weeks of pregnancy, was a consistent finding in abnormal cases and an immediate precursor of either toxemia or death of the offspring. This change was preceded by evidence of a rate of increase in the production of the placental steroids such as normally develops only after the 36th week, this earlier abnormality being apparent at least 10 weeks prior to the clinical accident and at least 5 weeks before any rise in serum C.G. The rise in serum C.G., when it occurs, therefore, may be secondary to a more fundamental deviation from the normal, the nature of which suggests premature ripening of the placenta with ensuing premature senility.

The significance of these findings in relation to attempts at preventive therapy is discussed.

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DIABETES MELLITUS ASSOCIATED WITH ALBRIGHT'S SYNDROME (OSTEITIS FIBROSA DISSEMINATA, AREAS OF SKIN PIGMENTATION, AND ENDOCRINE DYSFUNCTION WITH PRECOCIOUS PUBERTY IN FEMALES)*

Report of Case†

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The association of severe diabetes mellitus with the bizarre symptom complex described in 1937 by Albright and his co-workers[1] seems noteworthy, particularly since both conditions conceivably may bear some relationship to a common factor, in this instance the pituitary gland. Association of the two diseases must be extremely rare as no similar report has been recorded in the literature. Dr. Isabel Bogan,[4] roentgenologist at the Baker Clinic, Boston, after reviewing our case with Dr. Albright, observed that although the latter has now collected more than 50 cases showing the bony changes of osteitis fibrosa disseminata, there have been no diabetics among them. The case is of further interest in that roentgenograms of the skull are suggestive of osteitis deformans, and in view of reports by Moehlig and others[3,7,14-17] that patients having Paget's disease frequently exhibit abnormal dextrose tolerance curves of diabetic type. In the original report by Albright, the peculiar distribution of the osseous and cutaneous lesions was attributed to a neurologic or embryonic defect; while the gonadal dysfunction, which may be entirely absent in males, was regarded as

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due to a disturbance of afferent impulses to the pituitary gland. The insensitivity of our patient to insulin might lend further support to this hypothesis.

Albright's graphic description of 5 cases showing the curious triad of apparently unrelated symptoms—osteitis fibrosa disseminata, brownish pigmented areas of skin, and endocrine dysfunction with precocious puberty in females—and the subsequent report[2] of 2 additional cases in 1938 established this syndrome as a clinical entity. It may occur in complete or incomplete forms, depending upon whether or not one or more of the classic features is lacking. The bony dystrophy that was defined clearly by Lichtenstein[12] in 1938 and termed "polyostotic fibrous dysplasia" is apparently identical in roentgenologic, clinical, and histologic appearance, but the cases originally described did not display endocrine aspects or skin pigmentation. The latter features may be relatively infrequent in this disorder, for they are mentioned in but 4 of the 36 cases collected by Uehlinger[19] and described in 1940 under the title "osteofibrosis deformans juvenilis."

The published literature was thoroughly reviewed and summarized in 1942 by Gorham, Campbell, and Rust,[10] of Albany, and by Falconer, Cope, and Robb-Smith[8] in England. Both have pointed out the great variety of titles under which earlier cases have masqueraded, *e. g.*, pubertas præcox und knochenbrüchigkeit, osteitis fibrosa cystica generalisata, osteodystrophia fibrosa, generalized xanthomatosis of bones, juvenile Paget's disease, fibrocystic osteitis, fragilitas osseum, polyostotic fibrous dysplasia, and even von Recklinghausen's neurofibromatosis. Gorham *et al.*[10] tabulated 32 reported cases of the complete syndrome, and listed 19 others which did not exactly conform to the criteria enumerated by Albright as characteristic but which were considered to represent the incomplete form of the disease. Twenty of these cases had been vainly explored for adenomata of the parathyroids, 5 of them on two occasions.

In the view of Falconer *et al.*,[8] the disease consists of a characteristic multifocal fibrous dysplasia of bone in association with endocrine disturbances which may vary in type but have skeletal precocity as the usual feature, and may include other less constant manifestations such as sexual precocity, thyroid disorders, and acromegalic changes. The case to be described is apparently the first instance in which the endocrine disorder has been diabetes mellitus; and, since the patient has been under our observation, this has been by far the predominant feature of the case.

Albright's syndrome usually appears insidiously in childhood and its active phase is terminated when adult life is reached, or when premature fusion of the ephiphyses occurs. Pathologic fractures, limp, pain, or deformities are first noted. Coxa vara and genu valgum are not unusual. The quiescent phase is slowly reached, the disease is not fatal, nor does it appear to be hereditary. The diagnosis must rest on the clinical aspects, roentgenologic appearance, absence of significant alterations from normal of calcium and phosphorus levels, and if doubt still exists, on bone biopsy. Kornblum[11] characterizes

the typical histologic findings as thinning of the cortex of the bone, replacement of marrow and spongiosa by dense, gritty, rubbery, fibrous tissue interspersed with poorly calcified bone spicules, and an absence of cyst formation. In discussion of Kornblum's paper, Albright stated that the Roentgen examination presents 3 features which distinguish this disease from osteitis fibrosa generalisata: (1) there are areas of increased density and overgrowth of bone as well as decreased density; (2) the condition is not generalized and one should be able to find parts of the skeleton which are perfectly normal; (3) the disease practically never involves the epiphyses.

Case Report. L.T.W. (22107), age 22, a white male, was admitted to the receiving ward of the Indianapolis City Hospital on March 5, 1943, in severe diabetic coma (Rabinowitch Severity Index, 12). For a week previously he had complained of pain and swelling over the right side of the face, of excessive hunger, thirst, and polyuria, and although his mother stated that he had been a known diabetic since 1940, he had never before been in coma. Three months earlier he had discontinued his daily dose of 36 units of protamine zinc insulin and all dietary restrictions on the advice of a faith healer.

Physical Examination. The appearance of the patient was remarkable in that his face was irregularly swollen, particularly on the right side where induration involved the eyelid and pus exuded from the inner canthus. His head was asymmetrical, with prominent superorbital ridges and large malar prominences. Respiration was typically Kussmaul in type and the breath reeked of acetone. The nasal mucosa appeared congested and there was a mucopurulent blood-tinged discharge from the nares, more marked on the right side. All the teeth were loose, as if set in swollen, spongy, bleeding granulation tissue. Pus and blood exuded copiously about each tooth. Both maxillæ were tender on pressure and there was right cervical adenopathy; the heart and lungs were not apparently abnormal nor were the superficial reflexes. The brownish pigmented areas on the skin (Fig. 1) were not regarded as significant at the time but were considered "birthmarks" on the statement of the patient's mother. Exophthalmos of moderate grade was observed after recovery from coma, and a smooth palpable thyroid.

A tentative diagnosis was made of diabetic coma, acute sinusitis, cellulitis of the face, pyorrhea alveolaris, and avitaminosis. Blood was drawn for chemical determination and separate doses consisting of 60 units of unmodified insulin and 40 units of protamine zinc insulin were immediately injected. Roentgenograms of the skull were made and the patient was transferred to the ward for further treatment.

Laboratory Findings. The initial blood sugar level was 546 mg. per 100 cc. The CO_2 combining power was 12 volumes %; urea nitrogen was 60; white blood count 9100. The urine was loaded with sugar and gave 4+ acetone and diacetic acid reactions. The first roentgenogram of the skull was not very satisfactory owing to swelling of the soft tissues of the face and inability of the patient to coöperate, but there was obvious loss of translucency of all visualized sinuses, associated with mottled density of the frontal bone which suggested to the roentgenologist frontal osteomyelitis originating in the region of the frontal or ethmoid sinuses, or pathologic changes such as might be associated with Paget's disease or some other osseous dystrophy.

Course. Treatment of the coma was successfully completed within the next 12 hours, using a total of 315 units of insulin, 6000 cc. of normal saline, and 3000 cc. of 5% dextrose. The next morning a diet consisting of carbohydrate 130 gm., protein 60 gm., fat 80 gm. (providing 1480 cal.) was instituted, with separate doses of insulin and protamine zinc insulin, governed by the period urine specimens and postabsorptive and postprandial blood sugar levels. The patient's diabetes proved difficult to control, which was anticipated and attributed to infection. The temperature varied from 100° to 101° F.

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for a few days, then subsided as the swelling and tenderness of the face receded, except for sporadic elevations which seemed to be related to dental manipulations attendant on treatment and extraction of some of the loosened, abscessed teeth. The diet was increased on March 16 to 150 gm. of carbohydrate, 70 gm.

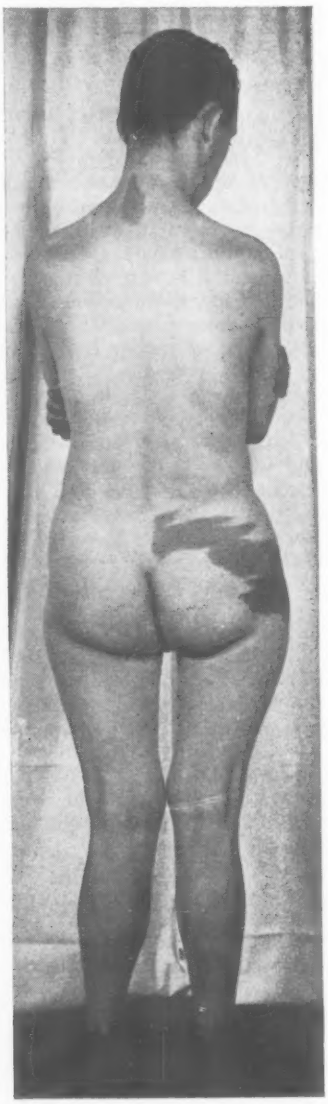

FIG. 1.—Areas of skin pigmentation. Note also the feminine configuration of the body and tendency toward genu valgum.

of protein, and 100 gm. of fat (1780 cal.), and on April 13th to carbohydrate 200 gm., protein 80 gm., and fat 120 gm. (2260 cal)., while the separate injections of insulin and protamine zinc insulin were redistributed into a single dose mixture given before breakfast in the morning. It was found that between 110

and 130 units in the ratio of approximately 3 to 1 (3 parts of unmodified insulin to 1 part of protamine zinc insulin) were required. Under this regimen, although not constantly sugar-free in all period specimens, control of fasting and postprandial blood sugar levels were reasonably satisfactory, for the patient was comfortable and demonstrated a progressive gain in weight and strength without hypoglycemic episodes. In the period from April 13th to July 1st, the average blood sugar level before breakfast was 136 mg. per 100 cc. and the afternoon postprandial levels averaged 142 mg. per 100 cc. (both taken twice each week).

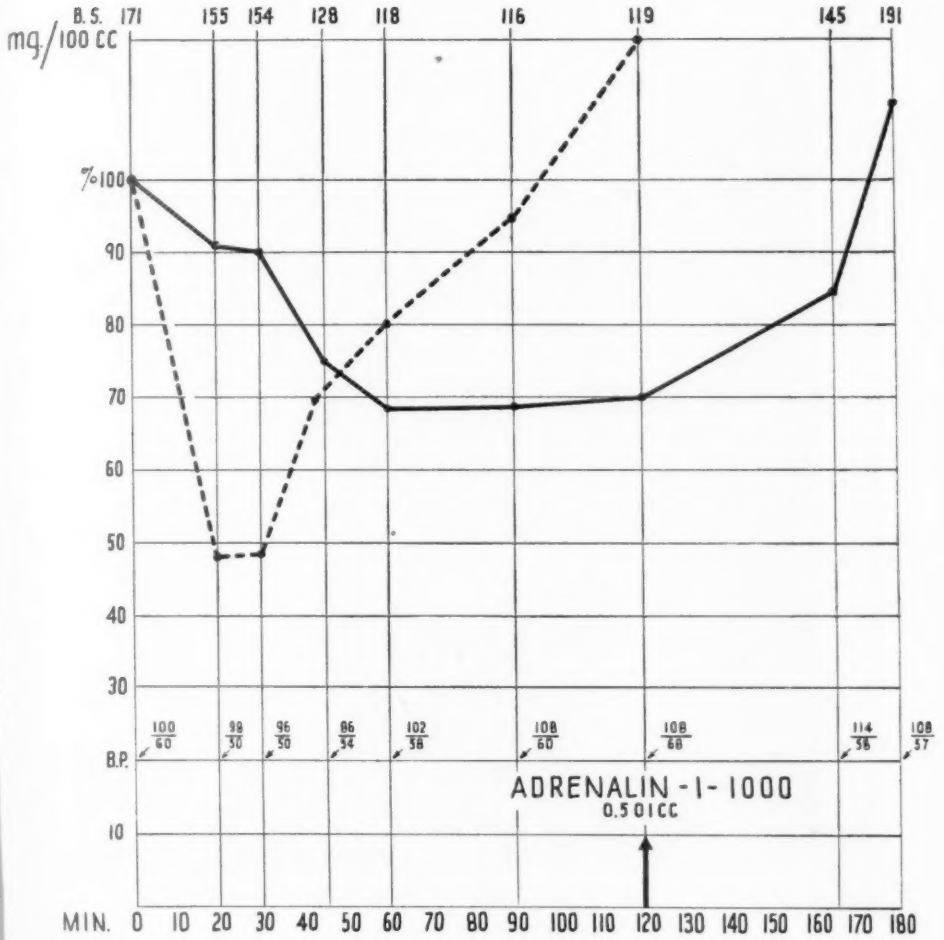

FIG. 2.—Insulin tolerance test. Broken line indicates composite normal. There is fairly marked insulin resistance followed by hypoglycemia unresponsiveness that is terminated promptly by elevation of blood sugar level after adrenalin.

Subsequent Laboratory Findings. The Kline and Kahn tests were negative; serum calcium was 9.1 mg. per 100 cc.; phosphorus 3 mg. per 100 cc.; total proteins 5.6 gm.; albumin 3.8; globulin 1.8; acid phosphatase 4.17 phenol units (King-Armstrong); alkaline phosphatase 77.2 phenol units (King-Armstrong); cholesterol 155 mg. per 100 cc. A month later the cholesterol was 150 mg. per 100 cc.; the alkaline phosphatase had fallen to 56 phenol units (1 unit = ap-

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proximately 1.8 Bodansky units). Basal metabolic rates were +32% and +42% on two occasions; recheck later was +45 and +22.

In view of the high insulin requirement, an insulin tolerance test (Fig. 2) was performed on March 22, 1943 (method of Fraser, Albright and Smith[9]). The dose was 0.1 unit per kilogram of body weight intravenously (6.3 units total).

Roentgen Examinations. Roentgen rays of the upper left molars showed recurrent caries, also caries of the upper incisors with blurring and loss of detail of the bone in the region of the incisors and remaining molar. Osteomyelitis was suspected. Later Roentgen rays of the head (Fig. 5), chest,

FIG. 3.—Roentgen ray of pelvis and lower spine made in 1935 (age 15 years).

pelvis, and left leg disclosed a marked enlargement of the middle and outer tables of the skull, giving the entire calvarium a mottled appearance. The frontal sinuses and most of the maxillary sinuses were obliterated; the facial bones were less involved. There was slight distortion and enlargement of the ribs, but not approaching the degree seen in the skull. There was no increased density of the lung fields, but a reduced radiolucency of the upper two-thirds associated with the reduction in the intercostal spaces. The pelvis (Fig. 6) showed marked cystic appearing areas as well as dense, irregular striations, and marked coxa vara. The pubic bones were less involved. The femurs and the left tibia also showed the same pathologic changes but to a lesser degree.

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There was evidence of old fractures of the ribs and the neck of the right femur. The scattered involvement of the skeleton as a whole is indicated in Figure 7.

Previous Admissions. Some interesting facts in the history of the patient came to light when earlier admissions under another name and number were traced. In 1932 the patient (age 12) was registered in the pediatric outpatient department, Indianapolis City Hospital, with the complaint of vomiting after eating vegetables, craving for sweets, and pain and burning in the feet. His mother stated that his appetite had always been capricious, and he

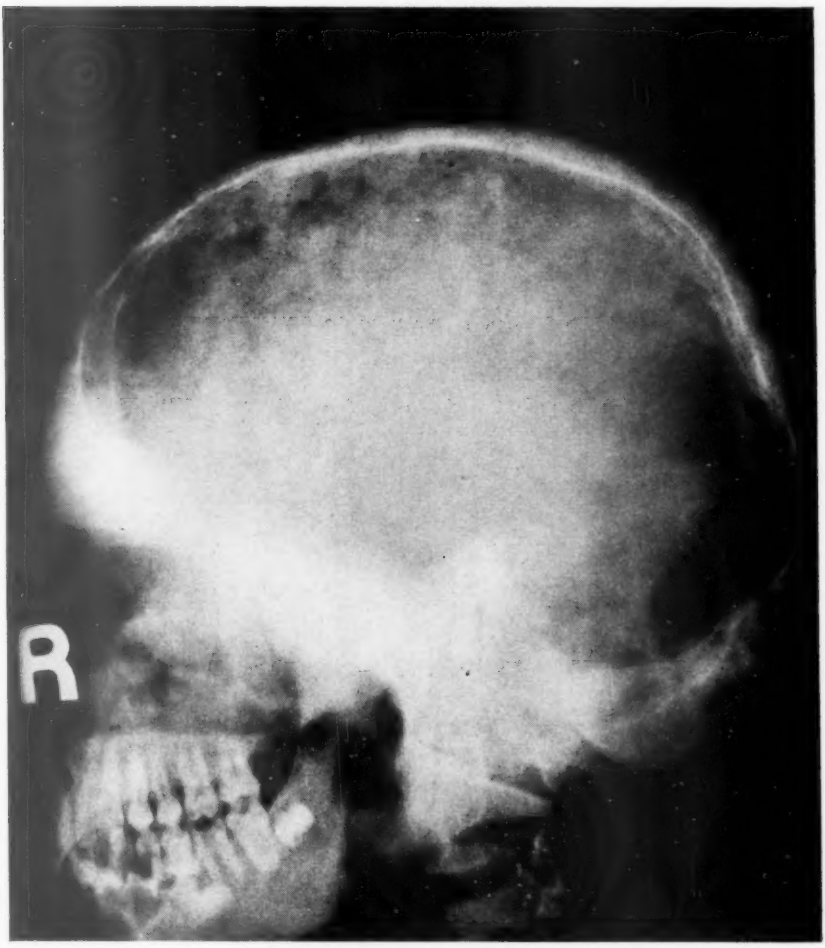

FIG. 4.—Appearance of skull in 1935 (age 15 years).

would eat no meat or dairy products but subsisted chiefly on sweet and starchy foods, and had had polyuria all his life. A note remarks the peculiar "Mongoloid facies" at the time. Viosterol and dietary corrections were prescribed. Although nocturia was present, the urine was negative for sugar. The patient was examined again on April 8, 1933 (age 13), at which time the complaint was a furuncle.

On June 27, 1935, the patient (then 15 years of age) was referred to the hospital by a private physician who had found a positive test for sugar in the

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urine. The complaint was painless limping for 2 or 3 years past, a crop of boils, nocturia 4 or 5 times, sudden spells of blackness before the eyes lasting a few minutes, and nocturnal pains around the thighs and hips. It was learned that one sister had died of diabetes mellitus at age 23. Examination disclosed some atrophy of the right thigh, the right hip was 2 inches higher than the left, and Roentgen ray (Fig. 3) revealed some cystic formations in the body of each ilium and a rather granular appearance to the bodies of the vertebræ throughout the dorsal and lumbar regions, suggestive of parathyroid dysfunction. Roentgenograms of the skull (Fig. 4) showed marked density in the

FIG. 5.—Appearance of skull in 1943 (age 22 years).

base, and thickening in all flat bones. There were unusual striations in the lower half of each femur which seemed due to islands of increased calcium deposition, resembling Paget's disease. The blood Wassermann and Kline tests were negative; blood sugar determinations were 104 and 80 mg. per 100 cc. The basal metabolic rate was +3; hemoglobin 100%; red blood count 4.72; white blood count 7050; blood calcium 10.5 per 100 cc.; phosphorus 3.6 mg. per 100 cc.; total proteins 6.9 gm. per 100 cc.

In 1937, fracture of the right femur occurred which was treated at another hospital.

The next admission was in 1940 (at 20 years of age). This time diabetes was well established as the blood sugar level was 421 mg. per 100 cc. in addition to the characteristic symptoms—the complaint was of photophobia, loss of sense of smell, and peculiar feeling of tightness of the flexor muscles of the hands and calves of legs. The latter symptoms had been present about 1 year. The patient's eyes were wide set and prominent, the face was now asymmetrical owing to hyperplasia of the left malar prominence, the skull appeared larger than normal, and absence of physiologic cup in the left optic disk was noted. At this time blood calcium was 11 mg. per 100 cc. and 9.9 per 100 cc.; phosphorus 5 mg. and 3.6 mg. per 100 cc.; blood proteins 7.2 gm., 6.5 gm., and 6.7 gm.; urine sugar was 4+; red blood count 4.8; white blood count 9400; Kline and Kahn tests negative. Roentgenograms disclosed marked widening of outer and middle tables of the calvarium owing to osteolysis and osteo-

FIG. 6.—Present appearance of pelvis and upper femurs (1943, age 22 years).

sclerosis. Involvement was particularly marked in the basal bones of the skull, those of the face, and the cervical vertebrae. A cystic character in this pathologic change was more apparent in the bones of the ilium and in the femurs. Definite coxa vara of both hips and a healed fracture (1937) of the right femur were evident. Roentgen findings suggested Paget's disease or osteofibrosa cystica.

A diet of carbohydrate 200 gm., protein 60 gm., and fat 130 gm., supplying 2210 calories, was instituted, and 20 units of protamine zinc insulin each morning served to control the diabetes adequately with normal blood sugar levels. The patient then again disappeared from observation until onset of diabetic coma constituting his present illness.

Progress since the last admission has continued uneventfully. There has been a gradual increase in weight and strength, but in spite of excellent diabetic

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control the insulin requirement has not declined materially (on December 9, 1943, the dose was 85 units of insulin with 30 units of protamine zinc insulin, mixed in the same syringe). The patient has returned to work, oddly enough, in a gymnasium, but is careful to protect himself from possible injury.

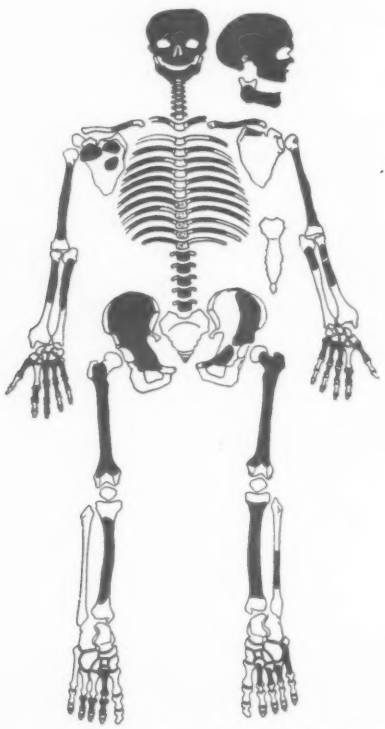

FIG. 7.—Main areas of skeletal involvement (1943).

Comment. The cause of this curious disease is unknown. Obviously it would be unwise to base any etiologic conclusions on this one case, which may or may not be merely a rare coincidence, since diabetes develops in one of 200 to 250 persons in the population and there is a history of diabetes in the patient's family. Nevertheless, it should serve to direct attention to what appears to be a common finding if it is looked for; namely, depressed glucose tolerance in certain of the osseous dysplasias such as Paget's disease. The appearance of severe diabetes and finally coma in our case, together with enlargement of the mandible as demonstrated by Roentgen ray, is suggestive clinically of acromegalia; while the exophthalmos, elevated basal metabolic rate, and goiter also point toward the pituitary as a factor. The insulin tolerance curve seems to support this possibility, and in addition the lack of responsiveness to hypoglycemia suggests adrenal involvement.

Recently Sternberg and Joseph[18] published the pathologic findings in the case reported several years previously by McCune and Bruch[18]

when the patient was 4 years old. Exophthalmic goiter was a prominent feature in this case, and it is pointed out that its occurrence as a part of the syndrome is significant enough to be other than coincidental. On autopsy the important endocrine changes were hyperplasia of the thyroid, thymus, and lymphoid structures, mature cystic ovaries, a narrow "lean" adrenal cortex, normal parathyroids, and the pituitary showed basophilic hyperplasia with adenoma formation. The picture was that of a gland showing evidence of prolonged stimulation and activity, especially of the basophil cells. When this case was originally reported there was slightly depressed glucose tolerance and glycosuria after 1.75 gm. of glucose per kilogram of body weight. No neurologic lesion was found. Cushing,[6] in describing the clinical manifestations of basophil adenomas, observed that exophthalmus, osteoporosis, and sometimes glycosuria were not infrequently associated with certain types of pituitary adenomata and that the diabetes in such instances was far more difficult to control than is that of pancreatic origin. No pituitary tumor was found in Coleman's[5] case, the only other autopsy reported thus far.

It is generally agreed that precocious puberty in females having the disease cannot be directly attributed to pituitary tumors. However, this type of precocious puberty is observed following hypothalmic lesions. Albright originally proposed that the characteristic triad of symptoms might result from an embryologic defect in the region of the hypothalmus. The facts that the areas of pigmentation have been present since birth of our patient, and that the osseous lesions were well developed at the time he first came under observation, seem significant in this connection.

Summary. 1. The first known case of diabetes associated with Albright's syndrome has been presented. Osteitis fibrosa disseminata, areas of skin pigmentation, and further endocrine dysfunction taking the form of mild exophthalmic goiter were observed.

2. Insulin resistance and unresponsiveness to hypoglycemia were demonstrated by the insulin tolerance test and are regarded as suggestive of a complex endocrine disturbance, possibly originating before birth, and implicating the pituitary gland.

NOTE: Since submission of this report another case, the 34th to be described in the literature, has been published (Dockerty, M. B., Meyerding, H. W., and Wallace, G. T., Proc. Staff Meet. Mayo Clin., **19**, 81, 1944). Although this patient showed precocious somatic development and menstruated at 7 years of age, she reached middle age before the disease was discovered, after a pathologic fracture. The status of the carbohydrate metabolism was not described.

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A NOTE ON IRRADIATION SICKNESS*

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Nausea, vomiting, headache, cramps and diarrhea which often complicate the course of therapeutic irradiation comprise the syndrome of Roentgen ray sickness reviewed lately by several investigators.[2,3,6,7] Our interest in the problem dates from the successful use of nicotinic acid in treating patients with these complications;[4] and the discovery that the behavior of urinary pigments and the codehydrogenases I and II following irradiation of the upper abdomen over the spleen resembled that in severely ill pellagrins.[1] As much evidence had accumulated to suggest other analogies between Roentgen sickness and certain dietary deficiency states, it was planned to make a comprehensive investigation of the effect of a standard dose of irradiation upon normal well-fed subjects; upon those given a vitamin B-deficient diet[5] with and without supplements of some of the vitamins in which the diet was deficient; and upon pellagrins and upon persons whose poor diet had caused ill-health without other stigmata of a specific deficiency syndrome. Studies on normal persons have not been reported previously. We are continuing this study but the results so far seem of sufficient importance to warrant publication at this time.

* The very heavy expenses of this study involving the special services of so many experts was made possible by the Research Corporation, the Nutrition Foundation, and Standard Brands, Inc.

† On leave of absence, Major, M.C., A.U.S., Armored Medical Research Laboratory, Fort Knox, Kentucky.

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Material and Studies. Of 16 subjects chosen for study, 5 were nutritionally normal persons hospitalized for some injury from which they were convalescing at the time of the experiment (2 white females, 1 white male, 2 colored males). One normal white male was treated after 6 weeks of control on the vitamin B-poor diet,[5] and again after a course of nicotinic acid. Three pellagrins (1 white female, 1 white male, 1 colored female), 3 persons with mild pellagra (1 white female, 2 white males), a white female with mild peripheral neuritis and 3 white females with subclinical vitamin B deficiency were irradiated under various conditions of vitamin therapy and dietary control.

The radiation was given in all instances after an overnight fast (13 to 16 hours after eating). An area over the spleen and upper abdomen was used. Four hundred Roentgen units were administered from a distance of 20 cm., using a Thorous filter, 200 K.V., 20 ma. at the rate of 33 R units per minute.

Tests for the codehydrogenase, biotin, riboflavin, pantothenic acid and nicotinic acid content of the blood were made before, and 6 and 24 hours after treatment in most cases. In some instances pyruvate and glutathione were determined. The urinary pigments were studied in daily 24 hour specimens before, and in 6 and 18 hour specimens after Roentgen ray.*

SYMPTOMS AFTER 400 R-UNITS TO UPPER ABDOMEN

			ANOREXIA	NAUSEA	VOMITING	HEADACHES	ABD. CRAMPS	DIARRHEA	PROSTRATION	SHOCK
W.F. - 40	(Subclinical deficiency)	control diet - 2 wks.	+	+	0	+	+	+	0	0
W.M. - 33	(Mild pellagra)	control diet - 3 wks.	+	+	+	+	+	+	±	0
		after 50 mg thiamin for 4 days	+	±	0	0	0	0	0	0
W.M. - 45	(Mild pellagra)	control diet - 15 days	+	+	+	+	+	±	+	0
		after 300 mg. Nic. Ac. for 4 days	+	0	0	0	0	0	0	0
W.F. - 36	(Mild neuritis)	control diet - 12 days	+	+	+	+	+	+	+	+
W.M. - 46	(Pellagrin)	Treated with 400 mg Nic. Ac., 50 mg thiamin +3 mg riboflavin daily for 1 mo.	0	0	0	0	0	0	0	0
C.F. - 40	(Pellagrin)	control diet - 14 wks 500 mg. Nic. Ac. - 6 wks.	0	0	0	0	0	0	0	0
		without Nic. Ac. - 6 days	+	+	0	0	0	0	0	0
C.M. - 42	(Normal)		0	0	0	0	0	0	0	0
C.M. - 59	(Normal)		0	0	0	0	0	0	0	0

FIG. 1.—Comparison of symptoms following Roentgen therapy in normal persons and those with mild or severe pellagra. In 3 of the deficient subjects the effects of irradiation with and without a preliminary period of therapy with thiamine or nicotinic acid are compared.

Results. Following irradiation of the type described above, the normal persons consuming a good diet or on various vitamin B supple-

* We are particularly indebted for the laboratory tests to Dr. and Mrs. Ansel Swain, Dr. R. E. Eakin, Dr. S. P. Vilter, Dr. Gwei Djen Lu and Mrs. Sue S. Sanders. Miss Monette Springer, R.N., and Mrs. Jane M. Mann, R.N. contributed most efficiently in applying methods to insure rigid restriction as to diet. The tests and normal diets were devised by Miss Jean M. Grant, Nutritionist, who also supervised the dietary controls. Prior to beginning this experiment she made a detailed dietary assessment of each patient and his family.

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ments had no ill-effects, except nausea in 1 white woman. The syndrome of irradiation sickness in varying degrees of severity occurred in the rest of the patients, including the normal person who had subsisted on the vitamin B-deficient diet[5] for 6 weeks. The symptoms in several subjects are recorded in graphic form in Figures 1 and 2.

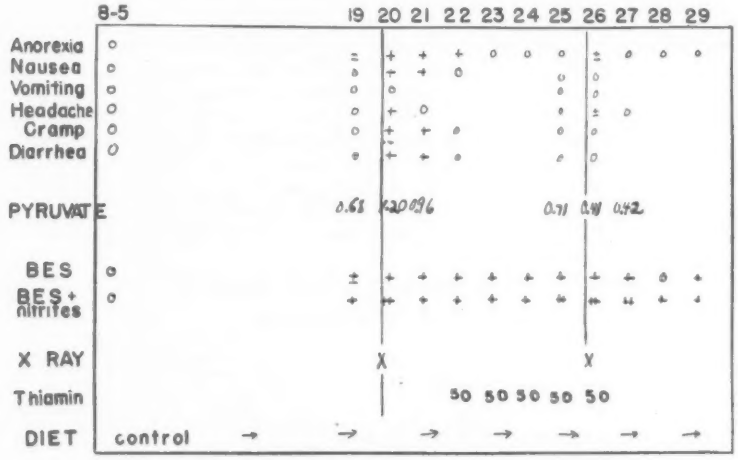

FIG. 2.—The effect of thiamine on reaction to irradiation. The control diet, one poor in B-complex vitamins, is the same as that used in previous experiments.[5]

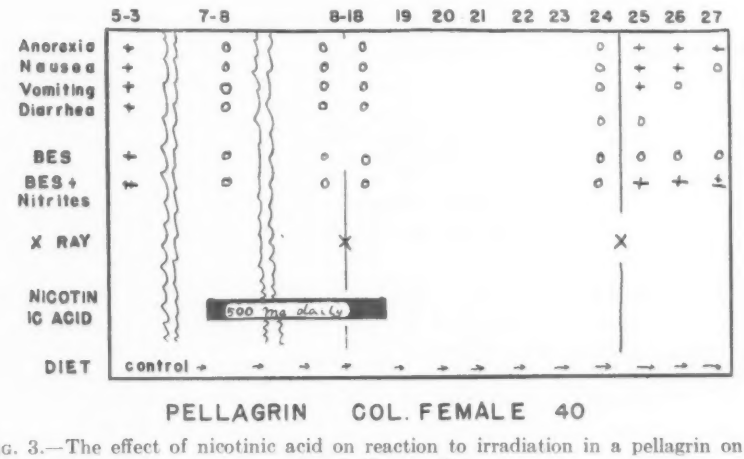

FIG. 3.—The effect of nicotinic acid on reaction to irradiation in a pellagrin on the vitamin B-poor diet.

Figure 2 shows also the result of pyruvate studies, and compares the results of irradiation before and after a supplement of thiamine. In Figure 3 the procedure was reversed. Roentgen therapy had no unpleasant effects after nicotinic acid had been given during the last 6 weeks of a period of more than 3 months on the control diet, but a

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week after the nicotinic acid supplement was discontinued the same amount of irradiation produced the characteristic reaction of Roentgen sickness. In all the cases studied there was a rough, but by no means exact, correlation between the severity of the reaction and the degree of vitamin depletion as gauged clinically. The most extreme reaction occurred in the woman with mild peripheral neuritis, who actually went into shock, with cold, sweating, cyanotic skin, impalpable pulse and systolic blood pressure of 80 mm. Hg. The man whose previous food habits were satisfactory had a mild and brief, though definite, reaction after 6 weeks on the vitamin B-deficient diet.

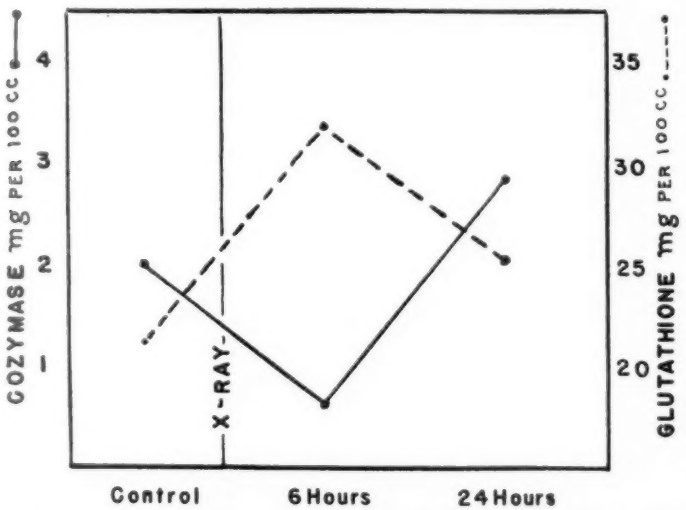

FIG. 4.—Changes in concentration of cozymase and glutathione in the blood of 2 subjects with pellagra following irradiation.

In some instances attempts were made to allay the symptoms by injection of large doses of thiamine or nicotinic acid, or both, but once the reaction was established these substances were of relatively little value, though it was our impression that they did help to a moderate extent. Other studies made in Cincinnati in which similar doses of the same vitamins were injected shortly before radiotherapy showed them to be relatively ineffective. When, however, a series of Roentgen ray treatments was given, and the irradiation syndrome occurred after the first treatment daily oral or intravenous vitamin B supplements were followed by a decrease in the distressing symptoms. Since the psychic factor is difficult to evaluate, control injections of physiologic solution of sodium chloride were tried, and not always without apparent help, so this phase of the problem needs more careful study on a much larger series of cases before conclusions are drawn. In the Birmingham study all subjects received tablets of some kind, so that they were not aware of the type of supplement and could not discriminate between placebo and vitamin except when the nicotinic acid produced flushing. A repetition of the experiment using the amide of

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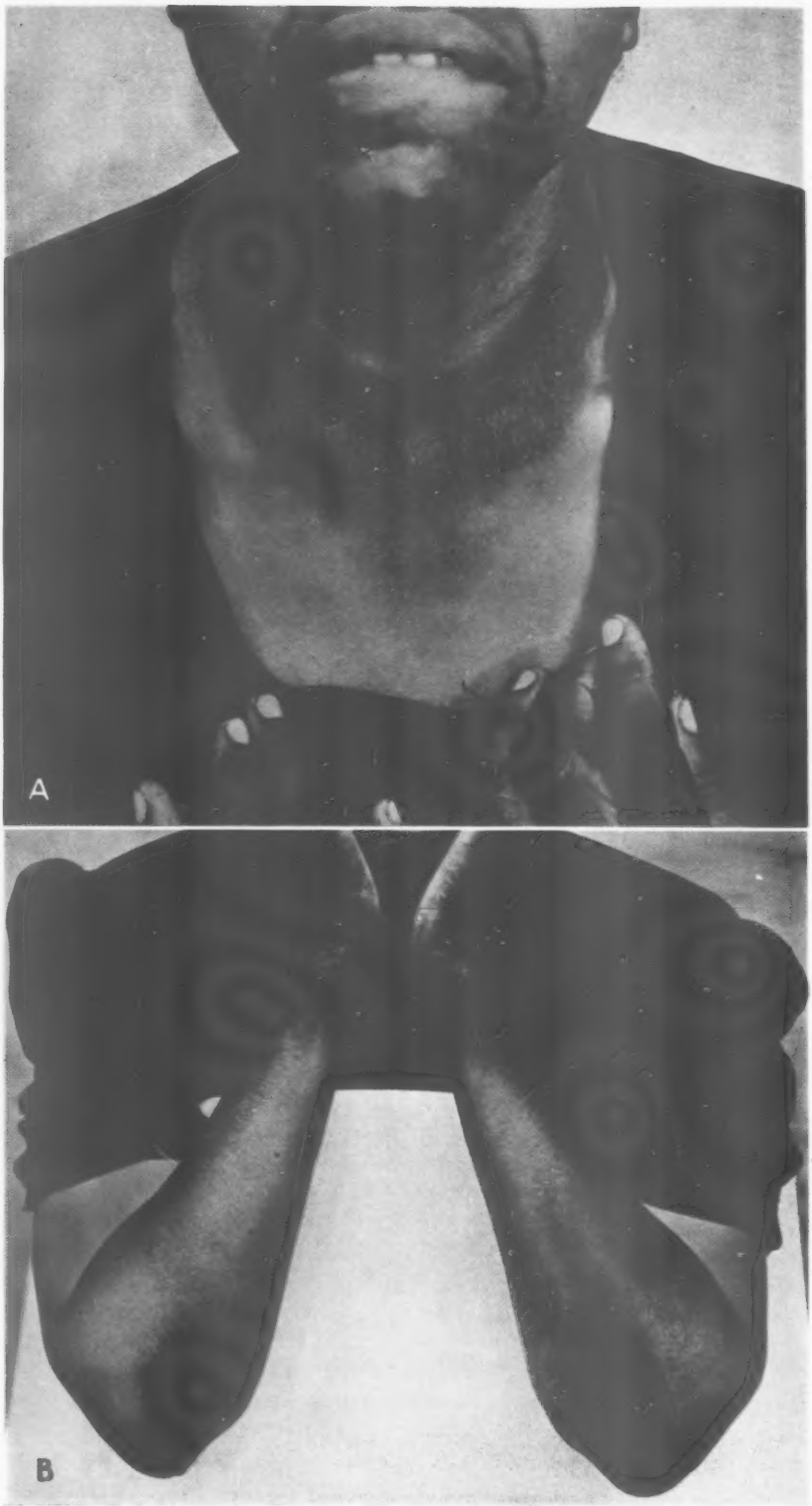

FIG. 5.—*A*, Classical example of Casal's necklace or cravat. Note also the forlorn mask-like facies. *B*, Symmetrical pellagrous dermatitis of the elbows, forearms and wrists over pressure areas.

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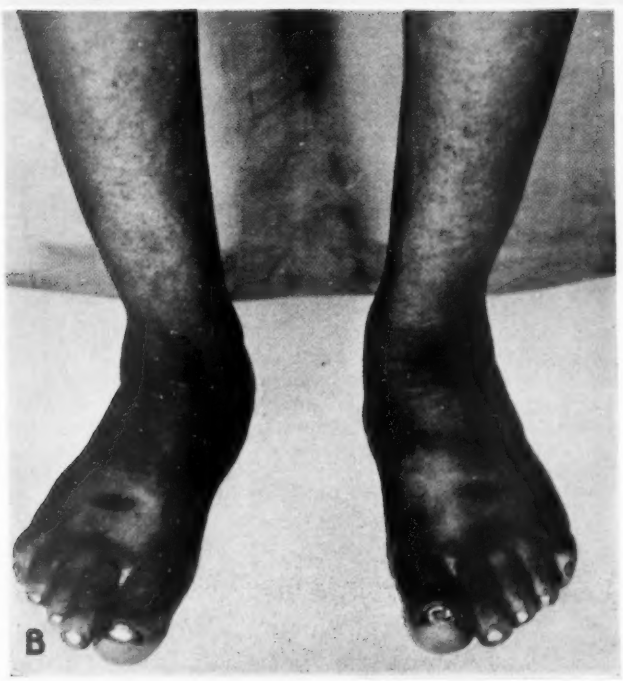

FIG. 6.—*A*, Dermatitis of the forearm and hand characterized by thickening and pigmentation of the skin. *B*, Bilaterally symmetrical dermatitis of the feet and ankles

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nicotinic acid has not been carried out but should be in order to eliminate the psychic element in the experiment.

Chemical Studies. There was no significant change in the blood level of biotin, pantothenic acid, riboflavin or nicotinic acid. Figure 4 shows the reciprocal relation of glutathione and cozymase levels. The fall in the coenzymes had been observed previously,[1] but the increase of glutathione or some similar reducing substance had not been noted before. Its significance remains obscure. The pigments in the urine appeared in excessive amounts, as had been found in a previous study.[1]

The above observations, under controlled conditions, suggested to the authors that we should include this representative case report of a patient who developed deficiency states following repeated Roentgen ray therapy:

Case Report. L. V., 41 year old negro woman, was brought to the Nutrition Clinic of Hillman Hospital in June, 1943, with a "breaking out" on the skin of 2 months duration.

F.H. and P.H. irrelevant.

P.I.: She was in good health until June, 1942, when she noticed for the first time abdominal pain and a bloody foul vaginal discharge. In August, 1942, she came to the Hillman Hospital and a diagnosis of carcinoma of the cervix, Grade 2, and of a large myomata uterii was made. Roentgen therapy was started and from then until April, 1943, 40 treatments were applied to the lower portions of the abdomen. Following each treatment she became severely ill. She developed nausea, vomiting and profuse sweating, and on 4 instances apparently went into "shock." This "*x*-ray sickness" caused her to vomit all food and water for 2 or 3 days and then for another day or two she had little or no desire for food. Accordingly, she ate little and retained rather little of that scant amount. Still later in the treatment (she does not remember just when) her desire for any food of any kind disappeared and by this time she did not go a full day without nausea and vomiting. Finally she took no solid food but frequently "drank strong coffee to give myself strength." About the first of May, 1943, she noticed large areas of deep pigmentation over the arms, feet, hands, legs and neck. The same day she noticed blurring of vision, excessive lacrimation and photophobia. Two weeks later she noticed severe pain and weakness and paresthesias of the legs and excruciating burning of the feet and ankles. At some indefinite time preceding this she noticed "trembles," "crawling sensations" of the flesh, became "fractious," screamed when she heard noises, and could not bear to see anyone. All these symptoms became even more pronounced during the first 2 weeks of May. She states that by this time she had become so sensitive that when anyone talked to her she cried and that her memory was so poor she could not go from one room to another in her own house without feeling lost. She said, "Doctor, you can never know how weak and dizzy and foolish-headed I am." In June, she developed burning and soreness of the mouth, tongue, throat, and salivation had increased to the point where she actually drooled large amounts. At this time she was having from 10 to 12 loose bowel movements daily.

She reported regularly to the tumor clinic until early in May when she became so weak a friend took her to her home. She left no forwarding address and efforts to locate her failed. Finally the friend became so alarmed about her condition she brought her to the tumor clinic. From there she was referred to the Nutrition Clinic and admitted immediately to the hospital for treatment.

Physical examination showed a well-developed, emaciated negro woman (the body weight had decreased from 247 to 129 pounds within a year). Large and small well-demarcated areas of crusted, deeply pigmented, inelastic kins covered the elbows, forearms, hands, knees, ankles, feet and scapulæ and

extended around the neck to form a collar of Casal (Figs. 5, 6). The tongue was edematous with transverse fissures, atrophic at the tip and edges with an occasional greatly hypertrophic red papilla. Neurologic examination showed greatly diminished muscle power and tone but no selective weakness. There was great increase in calf and peripheral nerve tenderness. Position sense was good. Vibratory sense was decreased approximately 30% in the upper extremities and 50% in the lower. Pin prick and light touch were normal.

Clinical impression: Characteristic pellagrous dermatitis, glossitis, stomatitis and nutritional peripheral neuritis (beriberi). The prognosis is considered that of carcinoma and myomata uterii.

Discussion of Case. Carcinoma and deficiency diseases are both notorious causes of loss of body weight but none of the visiting physicians or Dr. Walter B. Frommeyer who studied this patient in great detail could see that the tumor process in the cervix could obstruct alimentation sufficiently to produce nutritional deficiency symptoms of the degree of severity seen in this case. Her diet had been satisfactory, and she had never had nausea, vomiting or loss of weight until after the Roentgen ray treatments. We learned years ago that when, for any reason, a great deal of vomiting or diarrhea occurred severe deficiencies are likely to develop very quickly. It appears that the tissues of the body gradually adjusted but there came a time in May (the usual season for the symptoms of pellagra to appear) when the body tissues could no longer adjust and lesions in every way typical of pellagra appeared. The fulminating type of pellagra seen in this case developed within a year whereas without the predisposing factors—nausea and vomiting—years of ill-health and frequent recurrences precede an attack of this type.

Summary. The effect of administering a measured quantity of irradiation to the left side of the upper abdomen has been studied.

Persons on a diet poor in the vitamin B complex developed Roentgen sickness, which could be prevented or reduced in severity, by giving supplements of nicotinic acid or thiamine for a few days before irradiation.

Well-fed persons had little reaction to the same dose of Roentgen rays which made the vitamin B-deficient persons sick.

The practical application of these results toward the prevention or reduction in severity of irradiation sickness by means of nicotinic acid and thiamine is suggested by these findings. A patient with carcinoma and myomata of the uterus is reported in considerable detail since she was given repeated Roentgen therapy which in each instance was followed by severe irradiation sickness. She was not given supplements of nicotinic acid or thiamine and subsequently developed classical pellagra and beriberi.

Conclusions. Though unqualified conclusions are not justified from the few cases it has been possible for us to study adequately, it would appear that the optimum time for vitamin therapy is before and not after the syndrome of irradiation sickness appears and that such therapy is essentially preventive in nature. If, as we have suggested,[1] the basic disorder in Roentgen sickness is a disturbance in respiratory enzyme systems, this approach to the problem deserves careful clinical

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application. The fact that nutrition is often deranged in persons needing radiotherapy makes the use of careful dietary and vitamin therapy logical, if on empiric grounds alone.

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A NEW PRACTICAL METHOD FOR SUBCUTANEOUS ADMINISTRATION OF HEPARIN

Preliminary Report

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In 1916, while working in Howell's Laboratory, MacLean[13] accidentally discovered a substance which proved to be highly anticoagulant. Howell recognized the significance of this substance, and in 1918 named it "heparin"[9] because of its abundance in the liver. The application of heparin to the treatment and prophylaxis of thromboembolic disease remained dormant, however, until Charles and Scott[2] succeeded in preparing a purified barium salt of heparin which afforded a practical source of supply. Schmitz and Fischer,[23] who worked independently in Copenhagen, also had succeeded in obtaining a pure brucine salt of heparin. As a result, extensive experimental and clinical trials of this pure heparin were carried out by various investigators, particularly Best and Murray[1,17–22] in Toronto, and Jorpes, Holmgren and Wilander[10] in Sweden.

The work of these investigators and of others[7,8,15,16,24] established the value of heparin in vascular surgery and in the therapy of phlebothrombosis and thrombophlebitis. The beneficial action of heparin in the therapy and prophylaxis of postoperative pulmonary embolism has also been stressed.[3–5] In view of its ability to inhibit, in adequate dosage, the formation of blood platelet thrombi, heparin has had extensive appeal in subacute bacterial endocarditis.[6,11,14] At the present time, the clinical application of anticoagulant therapy in war surgery is of paramount importance.

A review of the literature indicates that anticoagulant therapy has been effective in a wide variety of conditions. Unfortunately, the

more widespread use of heparin, admittedly the safest and most rational of the anticoagulants, has been retarded by the necessity for its administration by continuous venoclysis or by periodic intravenous injections as suggested by Crafoord and Jorpes.[3] Of these two methods of administration continuous venoclysis is preferable due to the ephemeral effect of the individual doses in the fractional method. However, continuous heparinization by venoclysis for protracted periods of more than 2 weeks is virtually impossible of accomplishment. Moreover, the expense entailed has been an important deterring factor because of the huge amounts of heparin required to reach therapeutic levels.

In reporting on a new method of administering heparin originally devised for animals,[12] it was stated that the method was being adapted for humans. This method of depositing heparin subcutaneously in animals was arrived at after numerous attempts with pellet and glass capsule implantation. This latter approach had to be abandoned because of erratic, unpredictable results, the necessity for instrumental procedure and the obvious impracticability of sustaining heparin effects over prolonged periods.

To accomplish a slower and more equable absorption of heparin, the Pitkin menstruum* was adopted as a vehicle. This menstruum was developed to regulate the rate of release of water-soluble drugs injected intramuscularly or subcutaneously. The ingredients are: gelatin, 15 to 30%; dextrose, 5 to 12%; acetic acid, 1 to 1.5%; distilled water, *q. s.*, to 100%. The viscosity of the menstruum, which is predicated on the concentration of the gelatin and dextrose, determines the rate of liberation of the drug; the greater the viscosity, the slower the liberation. In the preparations containing heparin the optimum percentages of gelatin and dextrose were 18% and 8%, respectively.

The menstruum is made so that it liquefies at 80° F. Below this temperature it remains in a solid state. Its preparation is a rather delicate procedure as some of the ingredients oxidize readily and deteriorate with heat. It is best to prepare the menstruum by first dissolving the gelatin in distilled water, with a moderate degree of heat and double the desired percentage strength. After the gelatin has been thoroughly dissolved in the distilled water, it is placed in a sterile container to which a negative pressure (vacuum) is attached in order to draw out the air bubbles before it is allowed to solidify. Twice a day for 2 days it is liquefied with moderate heat, never over 110° F., and subjected to the negative pressure while in the liquid state. On the 3rd day it is liquefied, and the dextrose and acetic acid, in excess, are added. The mixture is then placed in a vacuum boiler and boiled for 15 minutes. When partially cooled (110° F.), sterile distilled water is added in sufficient amount to bring the percentage strength of the gelatin, dextrose and acetic acid up to the desired level. At

* We wish to acknowledge with thanks the kindness and coöperation of the late Dr. George P. Pitkin in furnishing us with details for the preparation of the Pitkin menstruum.

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this time the eucupin dihydrochloride is added for its anesthetic and antiseptic properties. The solution is again placed under negative pressure and allowed to solidify. It is liquefied daily for 5 days and bacteriologic tests made. If free of contamination at the end of 5 days, the heparin, epinephrine hydrochloride, ephedrine sulfate and chlorbutanol are then added. The preparation, while in a liquid state, is distributed in 1 to 2 cc. sterile ampules which are immediately sealed in the usual fashion with heat. The ampules are again subjected to the routine bacteriologic tests. From the moment the gelatin is dissolved, all utensils, containers, ampules and so forth must be sterile and the solution handled thereafter with aseptic precautions. After the eucupin, heparin, epinephrine, ephedrine and chlorbutanol have been added, the temperature should never be raised above 110° F. The preparation when ready for use is of a light amber color.

Ampules containing varying proportions of heparin* and Pitkin menstruum with or without vasoconstrictor elements, were prepared. All ingredients apart from heparin were found to be inactive in control tests.

The contents of the ampules were liquefied at 110° F., drawn up through a 2½-inch, 19-gauge needle into a previously warmed, sterile 5-cc. or 10-cc. syringe and immediately injected subcutaneously, preferably in the anterior or lateral aspect of the thigh. Intragluteal injections were also done in a limited number of instances. Although this method of administration was abandoned because of too rapid absorption, further experience may eventually prove it to be just as effective as by the subcutaneous route. When 2 ampules were employed, the contents were thoroughly admixed in the syringe before injecting. The material congealed promptly following inoculation. The injections were administered with a minimal amount of discomfort to the patient. Some patients subsequently complained of pain, tenderness, and swelling at the site of inoculation, particularly when a large amount (3 to 4 cc.) of the menstruum was used. This, however, did not prove to be a deterrent to further treatment, and symptoms promptly subsided upon cessation of therapy.

The initial formula (LP) contained 100 mg. of heparin (Table 1). During extensive trials† with this formula, it was found that at times there was a preliminary lag of several hours before any appreciable rise in coagulation time developed. This was then sustained to varying degrees for periods of from 2 to 5 days (Chart 1). In most instances there was a prompt rise and in some a sharp drop to the control levels. In these latter cases the crystals of heparin could be seen floating freely within the menstruum and were not strictly incorporated in the vehicle. The rapid absorption of these crystals resulted in a short-lived heparin effect. In other cases, following a preliminary sharp rise and fall in coagulation time, there was a secon-

* We are indebted to the Roche-Organon Company for their generous supplies of heparin.

† We wish to thank Dr. J. Rosenthal of the Jewish Hospital and Dr. A. M. Rabiner of the Jewish Sanitarium and Hospital for Chronic Diseases for permitting us to utilize their service cases for this phase of our work.

dary rise and more gradual fall to the base line. In these cases it was assumed that the heparin was partially in solution, the primary rise being due to prompt absorption of the free crystals; the secondary effect was ascribed to the more even and slower absorption of the menstruum with its dissolved depleted heparin. Experiments were also carried out in which heparin was administered intravenously at the same time or shortly after the LP formula was given subcutaneously. In these "primed" cases, there was a rapid rise in the coagulation time and precipitous fall which was then followed by a more sustained effect as the LP material was absorbed.

TABLE 1.—HEPARIN-PITKIN FORMULÆ

	LP (mg.)	LP–8 (mg.)	LP–9 (mg.)	LP–10 (mg.)	LP–11 (mg.)
Cryst. sodium salt of heparin	100.0	200.0	100.0	100.0	200.0
Epinephrine hydrochloride	1.0	1.0	1.0		
Ephedrine sulfate	25.0	25.0	25.0		
Chlorbutanol	0.5	0.5	0.5	0.5	0.5
Eucupin dihydrochloride	1.0	1.0	1.0	1.0	1.0
Pitkin menstruum *q. s. ad*	1.0 cc.	2.0 cc.	2.0 cc.	2.0 cc.	2.0 cc.

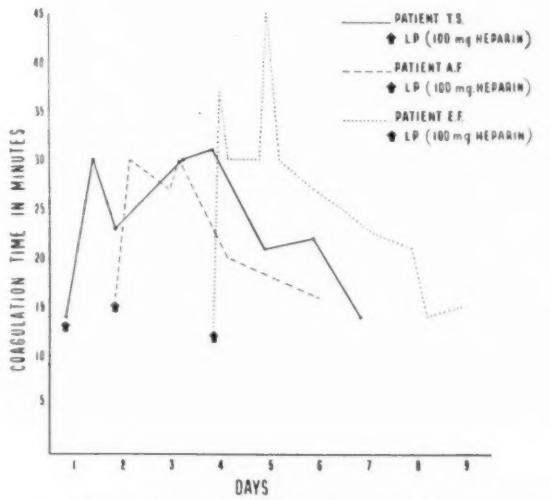

CHART 1.———— *Patient T. S.* Injected with LP (100 mg. heparin). Note sustained augmentation of coagulation time for 5 days. – – – – *Patient A. F.* Injected with LP (100 mg. heparin). Elevation of coagulation time for 3 days. ..... *Patient E. F.* Injected with L.P. (100 mg. heparin). Note 4-day heparin effect.

In order to overcome these shortcomings, the formulæ were revised (LP–8, 9, 10, 11; Table 1). The amount of Pitkin menstruum was increased to 2 cc. in order to accommodate the greater dose of heparin. LP–10 and LP–11 (Table 1) were devised so that the dose of heparin could be stepped up without adding to the vasoconstrictor elements.

The effects of formulæ LP–8, 9, 10 and 11 were evaluated singly and in combination in the course of 242 experiments performed on 51 patients. Some of these served merely as controls. Many patients suffering from thrombophlebitis, phlebothrombosis or subacute bac-

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terial endocarditis have been and are still being satisfactorily heparinized by this method.

It was possible by combining the various formulæ to initiate heparinization with liberal doses of the drug and then to maintain adequate heparinization with smaller doses or by spacing the injections. This has been done in actual practice, so that satisfactory results have been attained over protracted periods (5 weeks) with but 2300 mg. of

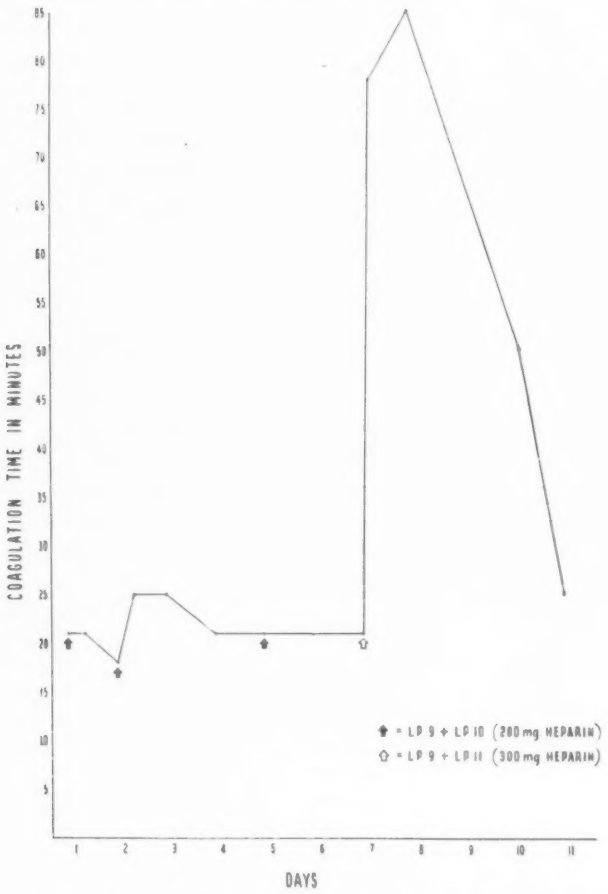

CHART 2.—*Patient T. G.* The repeated injection of 200 mg. heparin resulted in little or no augmentation of the coagulation time. The injection of 300 mg. heparin, however, yielded a prolonged effect which extended over 3 days.

heparin (Case 1). This contrasts with a comparable requirement of at least 10,500 mg. of commercial heparin were it at all possible to administer it by the cumbersome technique of continuous venoclysis.

Although no precise quantitative investigations were carried out, the impression was gained that heparin requirements paralleled body weight. This is illustrated in Chart 2. This patient, a tall individual weighing 190 lbs., responded little or none to the repeated injection of

200 mg. of heparin (LP–9 and 10). The injection of 300 mg. (LP–9 and 11), however, resulted in a rapid and sustained effect.

Representative cases demonstrating therapeutic applications of this method of heparinization over prolonged periods are the following:

Case Studies. CASE 1. *Thrombophlebitis of veins of pelvis and lower extremities* (Chart 3). D. S., a white female, aged 24, was admitted to the Jewish Hospital, service of Dr. E. L. Shlevin, on 1/9/43, complaining of fatigue, low-grade temperature, anorexia and loss of weight. She was delivered of a stillborn, 9½ month fetus on Oct. 30, 1942. Her postpartum course was

A *B*

FIG. 1.—Venograms of lower extremities of Case 1. *A*, Right lower extremity. There is an accessory saphenous vein present. Beading in the column of opaque medium (see arrow) is noted. This is indicative of the presence of multiple thrombi. None of the opaque medium enters the popliteal, posterior tibial, or femoral veins. These findings indicate an extensive thrombotic process involving these vessels. *B*, Left thigh. The popliteal vein is outlined to a point about 5 inches above the knee joint (see arrow). Beyond this point dye cannot be demonstrated although a considerable amount has passed into the upper portions of the saphenous vein. These findings indicate obstruction in the deep femoral vein in its upper two-thirds.

uneventful until November 15, when she developed swelling of the right leg, pain and fever. She was treated with bed rest, but the symptoms persisted. The swelling of the leg progressed and the temperature did not recede. She was then given sulfathiazole and sulfadiazine. The temperature regressed slightly with chemotherapy, but edema of the lower extremity spread to the thigh and groin. On December 12 the patient was allowed out of bed. The next day the temperature rose to 103° F. Sulfadiazine was again given and continued to the time of admission. She complained also of nausea, vomiting,

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backache and slight dry cough. *Physical examination:* On admission the patient appeared well developed and well nourished. The temperature was 102° F., pulse 100 and blood pressure 120/80. Both extremities were swollen and edematous and there was pelvic tenderness. *Clinical impression:* A diagnosis of thrombophlebitis involving the veins of the lower extremities and pelvis was made. Venograms were done on 1/15/43 (Fig. 1). These showed obstruction of the deep left femoral vein in its upper two-thirds. Right venography revealed multiple thrombi in the saphenous vein adjacent to the lower portion of the femur and extensive thrombotic involvement of the femoral, popliteal and tibial veins. Chemotherapy was discontinued, and heparin therapy was instituted on 1/16/43 by administering subcutaneously 2 cc. each of LP-9 and LP-10 containing a total of 200 mg. heparin. From a control level of 14 minutes, the coagulation time rose to 55 minutes within 24 hours. It was maintained continuously between 45 and over 75 minutes; averaging about 55 minutes. Injections of 200 mg. of heparin were given on

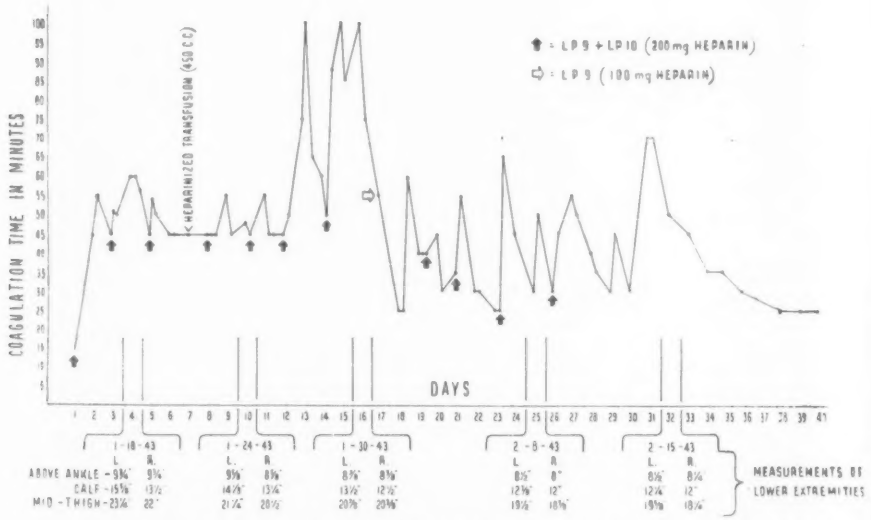

CHART 3.—*Patient D. S.* Thrombophlebitis of pelvic and femoral veins treated with heparin administered by the subcutaneous route. Therapy was continued successfully for 5 weeks. A total of only 2300 mg. of heparin was required.

an average of every 2nd or 3rd day. *Clinical course:* The temperature dropped dramatically following cessation of chemotherapy, and remained within normal limits except for an occasional rise to 100° F. The measurements of the lower extremities were as recorded on Chart 3. The clinical response to heparin therapy was highly satisfactory. There were no additional therapeutic measures except for a transfusion of 450 cc. of heparinized blood on 1/21/43 to combat moderate secondary anemia. There was a slight febrile reaction to the transfusion. Of interest was the successful heparinization over a period of 5 weeks requiring a total of but 2300 mg. of heparin

CASE 2.—*Phlebothrombosis, postoperative.* M. G., a white male, aged 44, was admitted to the Jewish Hospital, service of Dr. Leo M. Davidoff, on 10/24/42, for laminectomy to remove a herniated intervertebral disk. The postoperative course was uneventful until 10/30/42 when the patient complained of pain in both lower extremities. On 11/18/42 severe pain and tenderness were present in the left thigh and leg. *Physical examination:* The circumference of the left thigh and leg was considerably greater than the right. Edema was also noted, which became more evident the next day.

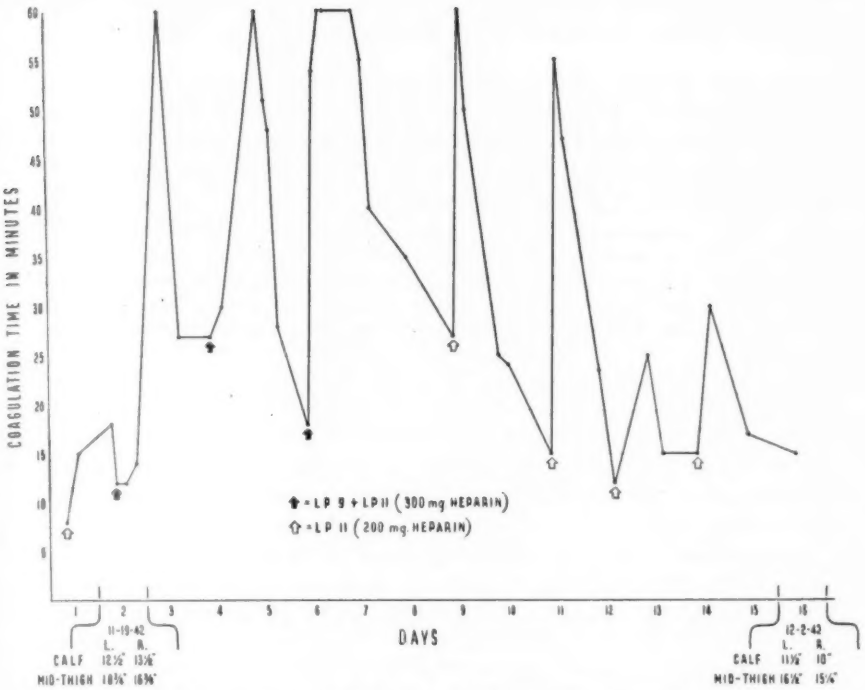

CHART 4.—*Patient M. G.* Postoperative phlebothrombosis treated with heparin administered by the subcutaneous route. Treatment was carried out for 16 days. A total of only 1900 mg. heparin was used contrasted with the usual requirement of from 4000 to 4800 mg. heparin by the intravenous method.

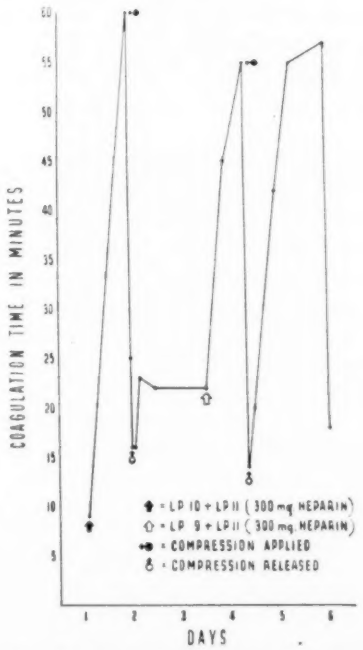
COAGULATION TIME IN MINUTES
= L P 10 + L P II (300 mg HEPARIN)
= L P 9 + L P II (300 mg. HEPARIN)
= COMPRESSION APPLIED
= COMPRESSION RELEASED
DAYS

CHART 5. *Patient H. T.* Effect of compression on heparin effect. Note precipitous drop in coagulation time with suspension of heparin absorption due to application of compression. Following release of compression, heparin is again liberated with resultant prompt rise in coagulation time.

Comparable measurements of both extremities may be noted on Chart 4, which also portrays graphically the progress of heparinization. *Clinical impression:* A diagnosis of phlebothrombosis of the deep venous channels of the left lower extremity appeared justified. Heparin therapy was advised and instituted on 11/19/42. *Clinical course:* A total of 1900 mg. of heparin was used over a period of 16 days. Coincidental with the heparin therapy there was a cessation of the phlebothrombotic process. After 1 week of heparinization, a marked improvement was noted in the leg with respect to the swelling and tenderness. This clinical improvement continued, and it was reflected by recession of the edema as indicated by the measurements (Chart 4). The patient was discharged from the hospital without residua.

Discussion. The therapeutic response portrayed by the foregoing cases has also been observed consistently in a number of other patients. These observations will be incorporated in a comprehensive clinical report. The present communication is devoted primarily to the description of a new method for producing a satisfactory heparin state that is safe, easily achieved, practical and economical.

As compared with our normal of 12 to 20 minutes for humans,* a coagulation time of from 30 minutes to 2 hours was considered an adequate heparin response. In practically every instance an acceptable prolongation of coagulation time was observed and the effects of a single deposit were apparent for 24 to 72 hours or more. On no occasion did any complications arise nor were any toxic symptoms noted. Despite the gratifying results obtained thus far with the formulæ at hand, additional experience may disclose the need for further revising the proportions of the various ingredients.

With the method of heparinization by continuous venoclysis, its mere discontinuance will result in a return of the coagulation time to normal within a few hours. For a more abrupt termination of the heparin state, the intravenous injection of whole blood or protamine has been advocated.

With the technique of subcutaneous administration of heparin as here described, no instantaneous withdrawal of the heparin effect is as yet feasible. However, whole blood or protamine may be employed to neutralize the free heparin, while compression about the site of inoculation will effectively suspend its further liberation. This was demonstrated in a case of subacute bacterial endocarditis successfully heparinized by our method. Injections were made as usual in the lateral or anterior aspect of the thigh. Compression was effected for 1 to 3 hours by means of a tourniquet above or a compression cup about the site of injection. Chart 5 depicts the precipitous drop in coagulation time which followed the compression and the prompt rebound which ensued with the release of compression.

Prolonged heparin therapy by the usual means of continuous venoclysis is economically prohibitive to a large group of patients regardless of its proven merit. The use of this subcutaneous method of heparinization, while not yet commercially available, gives promise of sharply

* The coagulation times in all instances were determined by the Lee-White modification of Howell's method. (GRADWOHL, R. B. H.: Clinical Laboratory Methods, St. Louis, C. V. Mosby Company, p. 514, 1943.)

curtailing the cost of this anticoagulant agent because of the reduced heparin requirement and ease of administration.

Summary. A simple, safe, and practical method for the subcutaneous administration of heparin has been devised. Its clinical application has been successfully attempted in 15 cases of thrombophlebitis and phlebothrombosis.

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MENINGOCOCCUS INFECTIONS WITH ARTICULAR COMPLICATIONS

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In these days, with meningococcic meningitis assuming importance as an epidemiologic problem, attention must be focused on one feature of the disease which is not sufficiently emphasized. Articular involvement of meningococcic etiology is not uncommon, and frequently presents important diagnostic and therapeutic problems. Although this complication has been by no means neglected in the literature, and an analysis of the subject by Herrick and Parkhurst[9] in 1919 represents an orderly approach to this confusing manifestation of the disease, nevertheless few publications are available since the introduc-

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tion of the sulfonamides. This is not, as might be suspected, because of the fact that the problem no longer occurs. Chemotherapy seems to have affected little, if at all, the incidence of joint involvement during the disease. Since meningococcic meningitis is again assuming importance in World War II, literature on this aspect of the disease is well in order.

Review of the Literature. The first clinical mention of the condition was given by Welch[23] as far back as 1810. In a report to the Massachusetts Medical Society, he spoke of "swellings . . . in some cases (of cerebrospinal fever) . . . in the joints and limbs . . . and their appearance has been compared to that of gout." This was over three-quarters of a century before the discovery of the meningococcus itself by Weichselbaum. North[14] mentioned "swelling like rheumatism of the joints." Still[22] and Gwyn[8] not only reported some cases, but demonstrated the organism for the first time in the joint fluid, blood and cerebrospinal fluid. The condition did not escape the keen, clinical eye of Osler[15,16] who reviewed the literature up to the beginning of the present century, and presented cases of his own experience. The French literature[19] contains many detailed descriptions. World War I afforded an excellent opportunity for study of the disease, and accordingly the most scientific accounts of the joint manifestations have resulted. Rolleston,[17] in England, and especially Herrick and Parkhurst[9] in the United States, have undoubtedly made the most valuable contributions to the subject. In the peace years between the last war and the present, little has been said outside of the reports of isolated cases by Jaffe,[10] Kobayashi,[12] and Campbell and Greenfield.[2] A few articles on the doubtful entity of postmeningitic spondylitis have also appeared. One exception on the relative silence on the subject was the article by Schein,[20] reporting on 23 cases of his own experience. Recently Cattell[3] gave the first report of meningococcal arthritis in a patient who had been treated with the sulfonamides. Their case, not dissimilar to the one presented here, was also found to yield purulent joint fluid on aspiration. They point out that "meningococcic arthritis with purulent effusion is a rarity." How much of a rarity it actually is, as well as other questions on the entire subject, will probably be answered by the medical workers in our Armed Forces.

Clinical Classification. We are indebted to Herrick and Parkhurst[9] for a practical classification of types of arthritis, but it must be realized that their classes are not always sharply demarcated, and also that several types may occur in the same patient, as in the case presented here. They spoke of 3 types.

Type A. In this group falls the "rheumatic" type of joint involvement, *i. e.*, the multiple-joint arthralgias occurring during the first few days of the disease as part of the general picture of the meningococcemia. It occurs simultaneously with the other features of meningococcic sepsis, notably the purpura. Pathologically, there is a purpura of the joints, so to speak, if Herrick is right in describing peri- and intra-articular hemorrhage as the cause (*cf.* section on pathology). Clinically the pain, redness, and tenderness are marked, though swel-

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ling is at a minimum. It is a symmetrical polyarthritis, affecting any of the joints. Its duration is short and frequently merely transitory, often being overshadowed by the usually dramatic picture of the primary disease, or overlooked in an irrational or comatose patient because of its subjective rather than objective character. Herrick was probably correct in considering these cases as particularly severe ones, but his grave prognosis for meningitis cases with Type A articular involvement no longer holds, for the severe bacteremia of these cases offers no special barrier to the marvelous sulfonamides. The joint manifestations may actually precede the meningeal (by as much as 2 months, according to Schein), and the patient then presents a picture of rheumatic or gonorrheal arthritis. The difficulties of diagnosis in such an instance are obvious; indeed, our Jamaican patient had joint symptoms a full day before these of the central nervous system, and it would have been impossible to have forecasted his meningitis at that time.

Type B. While the ankle involvement in our patient definitely belongs in Type A, his knee joint lesions are an excellent example of this B group. Here the arthropathy has its onset later in the disease, usually after the 5th day. It is usually monoarticular (if more than one joint is involved, one takes precedence over the others), and the knee is the joint most frequently involved. Effusion is the predominating feature of this type. Pain, redness, tenderness, and limitation of motion are reported by most observers to be *characteristically* at a minimum; but we find ourselves in complete agreement with Schein[20] and Cattell[3] that the effusion is by no means silent in all cases. Herrick and Parkhurst[9] felt that this arthropathy occurred in mild cases of meningitis, and they considered the general prognosis of the patient to be good. We have not found this complication to be dependent on the severity or mildness of the disease; and the reason for their favorable outlook was probably because of the fact that if the patient had survived up to the appearance of the complication, his natural powers of resistance would probably carry him through the rest of the disease. Meningococci are reported to be found in the joint fluid in one-third of the cases. The fluid itself may be mucinous, serous, seropurulent, or frankly purulent. Pathologically it appears to be an infectious lesion, in contrast to the hemorrhagic character of Type A joints (*cf.* section on pathology). Its duration is relatively long, and occasionally it is not without lasting effects on the joints themselves.

Type C. Herein fall the cases of arthralgias and arthropathies occurring as part of the well-known serum sickness. Its importance is small now that serum therapy of meningitis has become outmoded. It is related in no way to meningococcic meningitis and may occur in any disease where serum is given. It is an aseptic, serous type of arthritis, an urticaria of the joints, so to speak. Signs and symptoms are moderate, duration is short, and the prognosis is excellent. Coca[4] found the incidence of joint pain in serum sickness to be 1 to 2%. Schick,[21] quoted by Schein,[20] stated that "articular pains seldom occur but can be intense and annoying, involving large or small joints, often

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only one joint, the conditions being marked by transience and absence of objective symptoms." As Schein points out, this type (which occurs after the 6th day following the serum injection by any route) has its onset at the same time as Type B. As there are no absolutely differentiating characteristics, it is difficult to be certain with which type one is dealing but, we must reiterate, this problem will no longer be of any concern.

TABLE 1.—ARTICULAR INVOLVEMENT IN MENINGOCOCCUS INFECTION

Patient	Sex	Age	Joint involved	Onset (day of disease)	Treatment (of primary disease)	Treatment of complication	Duration	Result
H. M.	M	7	Lt. elbow	7th	Serum—intramuscular, venous, thecal	Aspiration (10 cc. purulent material)	2 wks.	Asymptomatic
W. O'C.	M	19	Rt. knee	5th	"	Conservative	Over 2 wks.	Sl. amt. of pain and stiffness in both knees on discharge from hosp.
			Lt. knee	6th				
E. S.	F	36	Lt. shoulder	7th	"	"	3 days	Asymptomatic
D. C.	M	20 mos.	Lt. knee	7th	"	"	2 days	"
C. C.	M	34	Both ankles	1st	Sulfathiazole	"	2 days	"
			Lt. knee	8th		Aspiration	2 wks.	"
			Lt. ankle	15th		Conservative	2 days	"
E. H.	M	39	Lt. knee	11th	"	"	10 days	"
J. P.	F	15	Both ankles	1st	Sulfadiazine	"	2 days	"
L. S.	M	20	Rt. knee	6th	"	"	2 wks.	Asymptomatic—but still slightly swollen
R. B.	M	3	Rt. wrist	15th	"	"	5 days	Asymptomatic
			Rt. knee	16th			1 day	"
L. H.	M	48	Rt. elbow	1st	Sulfathiazole	"	3 days	"

Postmeningitic Spondylitis. This doubtful entity was described by Epstein,[6] and later by Billington.[1] In view of its rarity and its occurrence always at the lower lumbar spine, it is possible that it is in reality a postpuncture affair, a cellulitis, a spinal osteomyelitis, or even, as Schein[20] suggests, herniation of the nucleus pulposus due to injury to the protecting annulus fibrosis by the spinal needle.

Sulfatoxic Arthritis. This entity, though rare, may make its appearance during the disease in view of our newer methods of treatment. Its rarity is attested to by the fact that authoritative reviewers of sulfonamide toxicities either fail to mention such an occurrence, or merely speak of transient arthralgias. Long *et al.*,[13] however, say: "Painful joints have been reported in the course of sulfanilamide therapy and we have noted several patients who have received sulfathiazole had exquisitely tender, swollen joints." They emphasize that this occurrence may confuse the treatment of gonorrhea because of its resemblance to gonorrheal arthritis. Glicklich and Sherman[7] report a very interesting case in which the arthritis was in all probability of chemical origin. This was a case of chancroidal infection, treated with sulfathiazole, in which the knees and elbows became tender and swollen with effusion. They aspirated 50 cc. of clear, sterile (on culture), serous fluid containing a few polymorphs per high-power field and 4.1 mg. per 100 cc. of sulfathiazole. Coincident with this were other manifestations of drug toxicity. The Ducrey lesions had disappeared by this time and the drug was stopped; the joint symptoms then sub-

sided. One week later, after a test dose of 3 gm. of sulfathiazole, the full picture of drug toxicity (including the joints) returned. The drug was stopped immediately, and the patient became asymptomatic in 12 hours. A high protein level (above 3.2%) of the joint fluid and a sugar content markedly lower than that of the blood definitely suggests an infectious rather than a toxic arthritis, but until more data is had on "sulfarthritis" this cannot be regarded as an infallible differentiating test.

We have spoken of Type A arthritis as purpuric, Type B as infectious, and Type C as urticarial. It is perhaps wrong to call the condition an arthritis. It is, rather, a synovitis, or at the most a periarthritis, but actual involvement of the osseo-cartilaginous tissues may occur. Keefer *et al.*[11] give the most recent and perhaps most accurate knowledge of joint lesions. "Meningococcic arthritis is a metastatic lesion involving first the deeper synovial tissues" (Type A of Herrick). "Later," (Type B) "infection invades the superficial cells with effusion of fluid into the joint cavity and varying degrees of destruction of the cartilage. It is essentially a metastatic acute synovitis." This, Cattell[3] implies, makes Herrick's[9] classification meaningless, since his Types A and B are but varying degrees of severity of the same "ens morbi." Even if this be true, and Herrick's grouping be worthless from a pathologic standpoint, it is still a most useful clinical classification. Certainly, much more study of the lesions postmortem must be done.

Incidence. Rolleston[17] of England reported an incidence of 4.8% of articular involvement in meningitis. Councilman *et al.*[5] reported 5.4%, Herrick's series showed 6.5%. A series at the Bellevue Hospital revealed an incidence of 7.7%.[20] Sainton[19] believes this complication to be much more common, occurring in some degree in one-fifth of the cases. At our South View Hospital 10 cases of arthritis have occurred among 266 cases of meningococcus infection within the past 12 years.

Four cases of articular manifestations occurred among 215 patients during the 10-year period previous to the advent of chemotherapy. Six cases occurred in the past 2 years among 51 cases of meningococcus infections treated only with sulfa drugs. The wide difference between 1.9% incidence before, and 11.8% occurrence since the use of chemotherapy may well be accounted for by the lessened mortality with more opportunity for complications during convalescence due to the life-saving benefits of the sulfonamides.

Case Study. The case of meningococcic meningitis presented here is of special interest, first in that it included two types of arthritis, and second because of the rare type of purulent articular involvement occurred after the meningeal infection had been cured by an adequate blood level of sulfathiazole. The patient was a 22 year old Jamaican who had been in this country only a few months. He was doing agricultural work at Winneconne, Wis., as part of the Government's effort to solve the manpower shortage problem. He became ill while at work and was taken to the Milwaukee County General Hospital with severe pain in both ankles as his chief complaint. Headache, sore throat, stiff neck, and fever were his other entrance complaints. Interestingly, 5 months before, while still in his native land, he developed ankle pain during

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the course of yaws. At this time he received arsenicals, and the joint pain disappeared. His main request now of the examining physician was for "another injection" to relieve his ankle pain.

Physical examination revealed a well-developed, well-nourished colored male who tossed about in bed during the examination and complained constantly of his head and ankles. His left pupil was large and round and did not react to light. The right was small and round and reacted. Ears and nose were normal. The pharynx was moderately injected, tonsils were small, and the teeth were in good repair. His head was held absolutely rigid, and attempts at flexion elicited an inconclusive Brudzinski sign. There was no cervical adenopathy. Examination of the chest revealed unrestricted respiratory excursions, normal lung resonance, normal breath sounds, and absence of râles. The heart size was normal, the rate moderately rapid and the rhythm regular. The abdomen was soft and non-tender; there were no palpable organs or other masses. Inspection of the ankles failed to reveal any evidence of pathologic change, but there was extreme pain on palpation and on active and passive motion. Patellar reflexes were absent bilaterally. Kernig's sign and the Babinski reflex were also absent. The temperature on entrance was 102.2° F. rectally, pulse 88, and respiration 20. Total white count was 16,600. On lumbar puncture, cloudy fluid under 25 mm. Hg pressure was obtained. This contained 18,075 leukocytes per c.mm. with a predominance of polymorphonuclear leukocytes. There were a few large gram-negative diplococci extra- and intra-cellularly, which proved to be meningococci on culture. Sugar was absent, protein 250 mg. per 100 cc., and chlorides 700 mg. per 100 cc. The patient was given 6 gm. orally of sulfadiazine in the first 8 hours and was then transferred to the South View Isolation Hospital.

Here he was placed on large doses of sulfathiazole orally. On repetition of lumbar puncture, cloudy fluid was obtained under slightly increased pressure, containing 8370 leukocytes per c.mm. (71% polymorphs, 29% lymphocytes). Smear showed numerous pus cells, few lymphocytes, and occasional gram-negative diplococci resembling meningococci (although culture was negative). Dextrose was 33 mg. per 100 cc., and protein 64 mg. per 100 cc. Blood and cerebrospinal fluid Kahn tests were negative. The urine was negative except for a trace of albumin, which, however, was absent on subsequent urinalyses. Six days after entrance, the total white blood count was 10,200 and 5 days later was 8520 with 64% polymorphs (53% segmented and 11% non-segmented), 28% lymphocytes, 7% monocytes, and 1% eosinophils.

On the 6th day of the disease, after having received 29 gm. of sulfathiazole, he developed marked pain in his left knee. This rapidly became warm and swollen, and on the following day 40 cc. of greenish purulent fluid were aspirated. The fluid contained numerous pus cells, but no organisms could be demonstrated on smear. In all, 350 cc. were aspirated on 5 occasions, and the fluid finally became serous in character and contained only a few pus cells. On the 12th day of the disease he developed a painful moderate effusion into the left ankle joint and at the same time a skin eruption, consisting of numerous small papules over the trunk and extremities. The drug was continued and the rash disappeared in 2 days, the ankle swelling subsiding, without aspiration, in 4 days. The blood level of sulfathiazole at this time was 11 mg. per 100 cc. and blood culture was negative. The joint fluid had a level of 310 mg. per 100 cc. of the total drug, and culture of the fluid was negative. On the 18th day of his disease, the patient was transferred back to the Milwaukee County General Hospital for convalescent care, completely asymptomatic, but with apparently a small amount of fluid in the left knee joint. Roentgenograms showed no significant change in either knee joint.

Discussion. Little has been said about the actual direct etiologic agent. The most likely explanation is a metastatic invasion of the synovial membranes by the meningococcus itself, these tissues acting as "loci minoris resistentiæ" during the septicemic stage. Herrick's observation of the presence of the bacteria in one-third of the joints

would seem to bear this out. However, one must wonder at the failure of the "sulfa" drugs to lower the incidence of the complication. Perhaps the infection becomes quickly localized and therefore resistant to the drug. Perhaps the joint lesion is a hypersensitivity response. Or maybe a symbiotic virus infection is the cause of the joint lesions. The possibility of one or more of the 12 strains of meningococcus being viciously arthrotropic must be thought of. Indeed, one is forced to speculate on the amazing similarity between the gonococcus and the meningococcus. The latter differs from the former in the ability to ferment maltose and in being less uniform in size. Otherwise the resemblance is startling. And, as a matter of fact, their tissues of predilection may be the same; the gonococcus can invade the meninges as well as the joints and the same is true for the meningococcus. Indeed, a case of urethritis resembling gonorrhea in every respect showed meningococci on bacterial examination. Sabah and Faham[18] reported a case of gonorrheal arthritis successfully treated with polyvalent antimeningococcus serum.

Summary. 1. The literature dealing with articular complications of meningococcus infections has been reviewed to date.

2. The incidence of articular involvement during the course of epidemic meningitis for patients at the South View Hospital has been compared with experience elsewhere.

3. In our series of 215 patients treated with sulfa drugs the incidence of arthritis was 1.9%, in comparison with an incidence of 11.8% arthritis among 51 patients receiving sulfonamides.

4. A case record of a monarticular purulent synovitis has been presented.

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PRIMARY AND SYMPTOMATIC AMYOTROPHIC LATERAL SCLEROSIS

A Clinical Study of 81 Cases*

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The contradictory results we obtained in our experimental investigation of the effects of vitamin E and other vitamins in the treatment of amyotrophic lateral sclerosis naturally raised the question whether the disease was one entity due to a constant etiologic factor or a clinical syndrome of varying etiology. To answer this question we studied intensively 81 patients personally observed between 1939 and 1942. Of this group we would designate 68 as primary; the rest, although also fairly typical clinically, we would regard as symptomatic. The two are discussed separately.

We did not include atypical or so-called transition cases, and rigidly excluded cases of progressive spinal muscular atrophy and lateral sclerosis, because we regard them as different entities. Most writers, it seems to us, are not definite on this point. The recent paper by Swank and Putnam[5] dealt with amyotrophic lateral sclerosis and "related conditions." In 1935 Petersen[3] reported on 22 cases. Dana's[1] older study of 70 cases obviously included a large number of progressive muscular atrophies.

Amyotrophic lateral sclerosis has always been regarded as a system disease involving the old and new motor systems, and it is known to follow a fairly consistent clinical course. As we studied the incidence of "types," the various modes of onset, unusual manifestations, possible etiologic or precipitating factors, and clinical variants, we began to doubt the unitary concept. All our patients were observed over long periods of time, up to 3 years, many to a fatal termination and necropsy, and we were able to study the life history of the disease. Without anticipating conclusions, we may indicate that our study justifies the tentative opinion that amyotrophic lateral sclerosis appears to be not one single disease entity but a syndrome of variable etiology, and that there are at least 3 different types which manifest themselves more or less the same clinically.

General Etiologic Factors. *Sex.* Table 1, giving the number of men and women according to age groups, shows a male-female ratio of

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2:1 in the primary group. The usual ratio is given as 3 or 4 to 1.[9] In the bulbar types, the sex incidence is said to be reversed, but this was not true of our 22 cases.

Age. Though practically all age groups were represented, the greatest number occurred between 30 and 69 (Table 1). The youngest case in our series was a girl 16 years of age and the oldest a man of 74.

TABLE 1.—DISTRIBUTION OF CASES ACCORDING TO SEX AND AGE AT TIME OF ONSET

Age	Men	Women	Totals
10–19	0	1 (16 yrs.)	1
20–29	2 (20, 23 yrs.)	0	2
30–39	10	5	15
40–49	12	7	19
50–59	15	6	21
60–69	7	2	9
70–79	1 (74 yrs.)	0	1
Totals	47 (70%)	21 (30%)	68

Nationality, Occupation and Heredity. Fourteen national groups were included in the series, but there were no Orientals and Negroes. All varieties of occupation were represented, without anyone predominating. There was no history of familial incidence of amyotrophic lateral sclerosis in any of the cases, so that hereditary factors can be excluded.

Other Etiologic Factors. Table 2 summarizes other possible etiologic factors which may be discussed in some detail.

TABLE 2.—POSSIBLE ETIOLOGIC AND PRECIPITATING FACTORS

	Cases
I. *Dietary and gastro-intestinal:*	
(*a*) Inadequate diet	3
(*b*) Marked weight loss, preceding onset	6
(*c*) History of gall bladder disease with restriction of fatty foods	3
(*d*) Restriction of diet because of "dysentery"	1
(*e*) Recurrent ulcer with gastro-enterostomy	1
(*f*) Unsuspected gastro-intestinal pathology discovered at postmortem	3
II. *Inflammatory:*	
(*a*) Severe upper respiratory infection at onset	2
(*b*) Syphilis	1
(*c*) Previous acute poliomyelitis	1
III. *Vascular:*	
(*a*) Diabetes	1
(*b*) Arteriosclerosis with thrombo-angiitis obliterans and coronary artery disease	1
(*c*) Marked generalized arteriosclerosis, clinically	5
IV. *Toxic:*	
(*a*) Exposure to gasoline	1
(*b*) Exposure to lead (painters)	2
(*c*) Exposure to heavy metals (electroplater)	1
(*d*) Spinal anesthesia	2

Dietary and Gastro-intestinal. Of 68 cases, 16 gave a history of dietary deficiency or gastro-intestinal dysfunction. The diets of 3 were definitely inadequate (Cases 7, 8, 32). Six patients (Cases 20, 44, 47, 48, 53, 67) gave a history of marked weight loss. Three patients (Cases 25, 38 and 41) had a history of gall bladder disease with restric-

tion of fatty foods from 1 to several years. One (Case 9) gave a history of restricted diet for 3 years because of diarrhea due to "dysentery." Another (Case 17), had a gastro-enterostomy for ulcer with recurrence 1 year before the onset of amyotrophic lateral sclerosis. Finally, in 3 of the 11 cases that came to necropsy, the unsuspected findings were carcinoma of the pancreas, perforated duodenal ulcer and cholelithiasis.

Inflammatory. In the primary group only 2 patients (Cases 27 and 32) gave a history of severe upper respiratory infections at the onset of their illness. One typical patient (Case 31) had a history of syphilis but developed the syndrome only after adequate treatment gave a serologically negative reaction. One patient (Case 20) had acute poliomyelitis at the age of 5 with a residual left foot-drop 31 years before the onset of amyotrophic lateral sclerosis. In the symptomatic group, there were a number which showed clinical signs and symptoms of inflammation of the nervous system.

Vascular. Despite the fact that we suspect a vascular etiology in some cases, and there is no doubt of this in certain bulbar types, few of our patients in the primary group showed evidence of vascular involvement. One (Case 32) had diabetes but without evidence of severe vascular disease. Another (Case 48) gave a history of thrombo-angiitis obliterans and coronary artery disease, and showed signs of generalized arteriosclerosis. Five others (Cases 29, 35, 40, 57, 58) showed clinical signs of marked generalized arteriosclerosis. In 2 of these, this was confirmed at necropsy. All had typical syndromes.

Toxic. None of the patients in the primary series showed any "toxic" manifestations, and, where suspicions were entertained, laboratory studies gave negative results. However, in the symptomatic group are recorded 2 cases following spinal anesthesia.

Trauma. This seems to us entirely fortuitous. In not a single instance was there anything to suggest an etiologic relationship between the trauma and amyotrophic lateral sclerosis.

Clinical Types. Tables 3 and 4 show the distribution according to "clinical types." Actually we feel that classification as to types adds little to the understanding of the problem, and merely describes localization in the nervous system. In our series the frequency of the various "clinical types" corresponds approximately to that reported by other authors.[3]

TABLE 3.—DISTRIBUTION OF 68 CASES ACCORDING TO CLINICAL TYPE

Type	Cases
Cervical	26
Bulbar	22
Quadriplegic	13
Lumbar	5
Hemiplegic	2
Total	68

Onset. The earliest manifestations of the disease recorded in our series are summarized in Table 4. The most frequent initial symptom was generally weakness of a hand or a leg, an arm or shoulder. Of

special interest was facial weakness as the initial symptom, and of the larynx as shown by impairment of the voice. The symptom of generalized weakness as a first manifestation occurred only in the bulbar group.

TABLE 4.—INITIAL MANIFESTATIONS OF AMYOTROPHIC LATERAL SCLEROSIS

	Cases
Lower extremities:	
Weakness, bilat.	9
Weakness, unilat.	8
Stiffness	1
Twitchings	1
Weakness and pain, bilat.	1
Upper extremities:	
Weakness, bilat.	3
Weakness, unilat.	25
Weakness and atrophy, bilat.	1
Weakness and atrophy, unilat.	8
Weakness and pain	4
Other sites:	
Hemiplegic weakness	1
Quadriplegic weakness	3
Marked generalized weakness	3
Bulbar:	
Voice changes	10
Dysphagia	7
Emotional instability	3
Dyspnea	2
Sialorrhea	2
Dryness of throat	2
Facial weakness	2
Pain in tongue	1
Pain in throat	1
Bitter taste	1
Nausea	1
Abdominal cramps	1

TABLE 5.—SIGNS OF PYRAMIDAL TRACT INVOLVEMENT

	Cases
Abdominal reflexes:	
Active	34
Weak	19
Absent	12
Absent, unilateral	3
Plantar response:	
Normal	22
Weak	9
Absent	6
Extensor (Babinski):	
Unilateral	12
Bilateral	19

Symptomatology. The signs naturally varied considerably according to the duration of the disease process. While, in general, weakness, atrophy and fibrillations tended to increase as the disease progressed, it was not uncommon to find marked weakness with little or no atrophy and fibrillations, or fairly marked fibrillations with only slight atrophy and weakness. In only one of our patients (Case 64) was there spasticity or an increase of tone in the upper extremities. In the lower extremities, especially in all the spinal types, spasticity or increased tone occurred frequently, but not invariably. A fairly common

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observation was the presence of marked hyperreflexia with pathologic reflexes and little or no spasticity. Hyperactive jaw jerks were found in 14 cases, and, as was to be expected, most frequently in the bulbar type. Table 5 shows that diminution or absence of the abdominals occurred in less than half the cases. This is an important and well known fact. The Babinski sign, too, was found in less than half the number of cases.

Unusual Symptoms. Somewhat unusual symptoms were found rather frequently. Thirteen patients showed fairly marked emotional lability with frequent forced laughing and crying; this included 2 (Cases 47, 48) in whom euphoria was more or less constant. An oily face and a relatively fixed expression was seen in 2 patients (Cases 42, 55). We also observed unusual ocular signs. Three patients (Cases 24, 29, 58) had irregular pupils, and bilateral ptosis was present in 3 (Cases 25, 29, 60). Nystagmus was found in 2 (Cases 22, 52), and weakness of convergence in 1 (Case 19). Facial weakness occurred in 12 cases; this was bilateral in 5 and unilateral in 7. Loss of voice was the first symptom in 2 patients. Marked sialorrhea occurred in 6 patients. Dryness of the throat as a persistent complaint was present in 2 (Cases 42, 57). There was bilateral loss of taste in 1 patient (Case 16). One (Case 44) had several attacks of vertigo, 3 complained of hesitancy in urination, urgency and retention (Cases 24, 29, 58).

Sensory Symptoms and Signs. Generally neither pain nor sensory signs are associated with the syndrome, but 32 patients gave a history of both. These are summarized in Table 6. Pain, burning, tingling, numbness and other dysesthesias occurred at one time or another. In most instances they were transitory, in 9 cases they persisted throughout the course of the disease. One patient (Case 55) had an appendectomy performed because of abdominal pain. Objective sensory disturbances, namely, involvement of the peripheral nerves and of the posterior columns, have been reported by Wechsler, Brock and Weil[6] and by Davison and Wechsler.[2]

TABLE 6.—SENSORY SYMPTOMS AND SIGNS IN AMYOTROPHIC LATERAL SCLEROSIS

	Cases
Subjective:	
Pain, numbness, burning, paresthesias	29
1. Preceding onset	5
2. At onset	3
3. During course	12
4. Throughout course	9
5. Abdominal pains	2
6. With onset of bulbar syndrome:	
Pain in throat	1
Pain in neck	1
Pain in tongue	1
Objective:	
1. Transitory loss of sensation—right median nerve	1
2. Hysterical hemi-sensory syndrome	1
3. Loss of vibratory sensation in lowers	1

Other Findings. Thorough general physical and extensive laboratory examinations were carried out on all patients. These included blood counts, urinalyses, blood chemistries, serologic studies, spinal fluid

examinations, gastric analyses, duodenal drainage, glucose and galactose tolerance tests, Roentgen rays of the skull, chest, large and small intestines, electrocardiograms, electroencephalograms and basal metabolisms. With the exception of the blood uric acid none of the findings showed any consistent deviation from the normal.[7] Considering the fact that for the most part our patients were in the middle and older age groups, the relatively few cases of general physical disease are noteworthy. Although mental symptoms, namely, psychotic manifestations, are recorded in the literature,[8] none of our patients in the primary group showed any. Spinal fluid studies showed no abnormalities in the primary cases, except for a not infrequent rise in protein, in 1 case as high as 84 mg. per 100 cc. Necropsy was performed in 11 cases. In all of these, the pathology was typical of amyotrophic lateral sclerosis. One case showed in addition evidence of old poliomyelitis.

TABLE 7.—CASES FOLLOWED UNTIL DEATH

No.	Type	Sex	Total duration (months)	Age at onset	Remarks
19	Bulbar	F	39	34	
20	Bulbar	F	8	36	
29	Bulbar	M	11	63	
35	Bulbar	M	22	64	
38	Bulbar	F	22	48	
42	Bulbar	M	36	42	Average duration, bulbar type: 20 months
47	Bulbar	M	21	35	
50	Bulbar	M	6	48	
52	Bulbar	M	23	53	
61	Bulbar	M	5	61	
30	Bulbar	M	26	36	
39	Bulbar	M	36	52	
23	Quadriplegic	M	25	23	
41	Quadriplegic	F	26	55	Average duration, quadriplegic type: 19 months
49	Quadriplegic	M	12	48	
58	Quadriplegic	F	13	56	
37	Lumbar	M	30	42	Average duration, lumbar type: 26.5 months
13	Lumbar	M	23	63	
40	Cervical	M	6	56	Average duration, cervical type: 14.7 months
44	Cervical	M	11	48	
8	Cervical	M	27	35	

Shortest duration, 5 months; longest duration, 39 months; average duration (22 cases), 19.6 months.

Course and Prognosis. Twenty-two of the 68 patients were followed until death. Table 7 summarizes some of the data on these cases. We wish to point out that while averages have some validity, they do not tell the whole truth. Thus, the average duration of the bulbar group was higher than that of the cervical. If, however, the 3 patients who survived 3 years are deducted, the average duration of the former drops below the latter. Furthermore, the larger number of deaths in the bulbar group shows that not only is the average duration less but the mortality is greater. Another point which is not evident from these averages is that while the average life expectancy is 2 years or less, quite a number of patients with amyotrophic lateral sclerosis live 3 or 4 or more years. This is true of all types, including the bulbar, although

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in the main, those with initial involvement in the lumbar cord are apt to live the longest.

No spontaneous remissions were noted in any of our cases. In the vast majority the course was inexorably downhill to a fatal termination. Although we are not concerned here with therapy, we wish briefly to record a few observations on vitamin E administration without drawing any conclusions. All patients received adequate doses of vitamin E during the period of observation. Fifty-three showed not the slightest effect; 15 seemed to show some favorable response. Seven of the latter (Cases 1, 5, 6, 30, 32, 41, 54) showed a temporary improvement in one or more groups of symptoms, after which they continued their downward progression. Four (Cases 4, 10, 43, 56) showed what seemed to be an arrest, in that there has been no noticeable progression. Four others (Cases 14, 24, 55, 62) showed actual improvement in one or more signs, an improvement which has persisted during the period of observation. There have been no cures and no recoveries.

Symptomatic Amyotrophic Lateral Sclerosis. As already mentioned, the cases in the primary group were rather carefully selected to include only those that showed the typical combination of upper and lower motor neurone disease. However, a number showed a clinical picture identical with or closely resembling amyotrophic lateral sclerosis, but they seemed to be related to specific etiologic factors. These we designate as symptomatic.

Encephalomyelitis. Two patients presented clinically a picture of amyotrophic lateral sclerosis in the course of diffuse inflammatory disease of the nervous system. Wimmer[10] long ago described cases of amyotrophic lateral sclerosis on the basis of encephalomyelitis. Although none of the cases included in the primary group gave a history of encephalitis, ocular signs occurred as unusual manifestations in 9 of the patients.

Case Studies. Case 1. G.R. (298058), a 52 year old housewife began, 4 months before admission, with sudden onset of unconsciousness which lasted for 3 days, followed by stupor and a temperature of 105° F. for 1 week. She then had diplopia which lasted for 2 weeks, was unable to speak clearly, had difficulty in swallowing, and weakness of all 4 extremities. Gradually the weakness of the left side of the body receded while that of the right side of the body increased, and speech disturbance grew more pronounced. One month before admission, fibrillations of the right upper extremity were observed.

Examination showed right hemiparesis with spasticity and increased reflexes. There were fibrillary twitchings of both upper extremities with atrophy of the intrinsic muscles of the hands, the right greater than the left. The speech was nasal; there was paresis of the soft palate on the right side and the tongue deviated to the left. The right pupil was slightly larger than the left and there was slight ptosis and facial weakness on the right. There was also a right hemi-sensory syndrome. Lumbar puncture revealed 8 cells; the fluid was otherwise negative.

Case 2. B.K. (441448–450202), a 49 year old woman was admitted to the hospital in May and in December of 1939. On the first admission, she showed a typical syndrome of disseminated encephalomyelitis. She began to recover and was discharged as improved. On the second admission, she showed, in addition to bilateral pyramidal tract signs, diffuse wasting of the muscles, especially of the hands, a picture which justifies the diagnosis of the syndrome of amyotrophic lateral sclerosis.

Syphilis. One of the cases included in the primary group gave a history that was definite for and showed pupillary signs that were characteristic of syphilis. Otherwise there was nothing to suggest an etiologic relation between lues and the typical picture of amyotrophic lateral sclerosis. In the following case the relationship seems to be present.

CASE 3. J.R. (341502), a 34 year old laborer, who contracted syphilis at the age of 27, developed bilateral wrist drop, which persisted unchanged despite adequate treatment. Examination revealed atrophy of the muscles of both shoulders, upper extremities and hands. There was generalized hyperreflexia with bilateral Babinski signs. The pupils were irregular and unequal; both reacted poorly to light and in accommodation. The blood Wassermann was negative.

Previous Acute Poliomyelitis. The relationship between poliomyelitis and amyotrophic lateral sclerosis has long been a matter of considerable interest.[4] In the 68 primary cases, we have one patient who gave a history of poliomyelitis at the age of 5. At the age of 33, she developed typical amyotrophic lateral sclerosis. The following 3 cases, not included in the larger series, showed clinical syndromes resembling amyotrophic lateral sclerosis. Two of them had acute poliomyelitis in childhood, while the third showed, at necropsy, also the typical pathologic features of poliomyelitis without a previous history.

CASE 4. M.S., (457784), male, aged 41 had poliomyelitis at the age of 2 and residual flaccid paralysis of the left lower extremity. He was admitted to the hospital because of drawing sensations in both arms and heaviness of the hands. Examination showed generalized hyperreflexia (except in the paralyzed left lower extremity), absent abdominal reflexes, and a right Hoffmann sign. There was atrophy of the muscles of both hands and of the left leg, but no fibrillations. Later he developed difficulty in walking, more marked hyperreflexia, a questionable right Babinski sign, increased weakness and atrophy of the small muscles of both hands, and occasional fibrillations. The spinal fluid protein was 153 mg. per 100 cc. The syndrome had lasted 8 years.

CASE 5. N.W. (459052), a 40 year old woman gave a history of poliomyelitis in early childhood, with residual paralysis of the right leg. She was psychopathic and had repeated admissions to mental hospitals. At 38, right facial weakness and "trembling" of the hands appeared, and over a period of 2 years atrophy and fibrillations of both upper extremities and early bulbar involvement set in. On examination she showed motor involvement of the 5th, 7th, 9th, 10th, 11th and 12th cranial nerves, generalized atrophy and fibrillations, lively left knee jerk but otherwise depressed deep reflexes, and absent abdominals. The spinal fluid was normal.

Aside from the old poliomyelitis and the psychosis, the course and the widespread involvement suggested a virus infection. During this time there was one period when the clinical picture closely resembled amyotrophic lateral sclerosis.

CASE 6. H.B. (475237), a 51 year old tailor developed progressive weakness of the right hand and to a lesser extent of the left hand, followed by hoarseness. On examination he showed generalized weakness, most marked in the right upper extremity, atrophy of both deltoid and pectoral muscles, and questionable atrophy of the right forearm and right thenar eminence. There were fairly marked fibrillations in both upper extremities, especially in the deltoid and pectoral regions. The deep reflexes were slightly more active on the right, especially in the upper extremity; the abdominals were slightly diminished.

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Six months later he began to have respiratory difficulty. He now showed a marked increase in the weakness of the upper extremities with pronounced atrophy and fibrillations, also weakness of the intercostal muscles, and weakness and atrophy of the thighs. The deep reflexes, except for the triceps jerks, were diminished; so were the abdominals. He died within 3 weeks. Necropsy revealed areas of hemorrhage and perivascular infiltration in the anterior portion of the spinal cord, most marked in the cervical region, with degenerative changes in the anterior horn cells. There were also some degenerative changes in the pyramidal tracts.

Toxic. Four of the patients in the primary group with typical pictures gave a history of exposure to toxic substances; namely, gasoline, lead and other heavy metals. However, in none were there toxic manifestations. In 2 patients a clinical picture resembling amyotrophic lateral sclerosis followed reasonably soon after spinal anesthesia to suggest a causal relationship.

Case 7. C.D. (446493), a 45 year old woman developed gradually increasing stiffness of both legs 3 months after an appendectomy performed under spinal anesthesia. On examination she showed weakness and spasticity of the right leg with hyperreflexia in both lowers, absent abdominals and a right Babinski and Chaddock sign. The stiffness and weakness of her legs gradually progressed for 2 years. She then noticed weakness of her right hand, followed by bulbar symptoms. Two months before death, she had weakness of all 4 extremities with atrophies and fibrillations, and marked bulbar symptoms with atrophy and weakness of the tongue. The abdominals were absent, the deep reflexes were active in the uppers and depressed in the lowers. There was a hyperactive jaw jerk.

Case 8. J.S. (423378), a 42 year old man received 3 spinal anesthetics for a multiple stage resection of a carcinoma of the rectum and sigmoid. While still in the hospital he began to complain of pain and weakness in the left arm and numbness of the left leg. Slowly, over a period of 4 years, he developed weakness of all 4 extremities and marked bulbar symptoms with bilateral pyramidal tract signs. During this period, he was admitted to the Johns Hopkins Hospital where a diagnosis of amyotrophic lateral sclerosis was made. His symptoms progressed steadily and he died 4 years and 3 months after the onset of his neurologic symptoms. Necropsy revealed central nervous system changes characteristic of amyotrophic lateral sclerosis.

Vascular. In none of the 68 cases included in the primary group was there conclusive evidence that vascular disease had direct etiologic relationship to the disease syndrome. The 5 cases which follow showed, we believe, such evidence. All but one ran a longer course than the primary cases of amyotrophic lateral sclerosis.

Case 9. R.R. (425295), a 58 year old woman began with pain in her legs and her hands. Later she developed weakness and progressive atrophy. Examination revealed weakness of all 4 extremities with atrophy and fibrillations of the left leg and of both hands. She had a nasal, monotonous speech and some difficulty in swallowing. All the deep reflexes were markedly diminished, but the Babinski sign was present bilaterally. Besides generalized arteriosclerosis, she showed evidence of myocardial damage. She was observed for 2 years, during which she had two attacks of congestive failure.

Case 10. L.W. (444014), a man aged 59, had had repeated hospital admissions over a period of 4 years because of peripheral vascular disease and arteriosclerotic heart disease. During this time he developed a combined anterior horn and pyramidal tract syndrome with atrophy of both hands, diminished abdominals, increased lower deep reflexes, and suggestive bilateral Babinski signs.

Case 11. P.F. (468180), a diabetic 58 year old woman began with weakness of her left hand, followed by weakness and stiffness of the right hand and both

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feet. On examination, she showed atrophy of both hands, but no fibrillations. The abdominal reflexes were absent, the deep reflexes in the lower extremities were hyperactive and there was a bilaterally positive Mendel-Bechterew sign. She had marked generalized arteriosclerosis.

CASE 12. J.O. (407557), a 60 year old woman, also a diabetic of long standing, began to have pain and weakness in all 4 extremities 2½ years before admission. Examination revealed weakness, atrophy and fibrillations of all 4 extremities. There was generalized hyperreflexia, absent abdominals, and bilateral Babinski signs.

CASE 13. M.H. (401480), a 48 year old man was known to have hypertension for 2 years. One year before admission to the hospital he began to have steadily progressing weakness of the left lower extremity. On examination he showed weakness of both lower extremities with some atrophy and fibrillations of both thighs. There was some weakness of the left hand. The deep reflexes were hyperactive, the abdominals were diminished, and there was bilateral Babinski sign with ankle clonus.

Comments. As stated in the introduction, we purposely excluded cases of progressive spinal muscular atrophy and lateral sclerosis, and for the following reasons. Amyotrophic lateral sclerosis is a disease of adult life and of middle and old age. We recorded only 1 rare instance below 20 and only 2 between 20 and 30. Progressive spinal atrophy is common in young people and lateral sclerosis, even excluding the familial group, also occurs at all ages. We realize, of course, that many cases beginning as "pure" pyramidal tract affections slowly or rapidly go over into multiple sclerosis, amyotrophic lateral sclerosis or other syndromes, but we are not here concerned with transition cases. Lateral sclerosis and progressive muscular atrophy are very slowly progressive conditions. Patients with either disease live for years and years, up to 20 and 30 or longer after the initial signs or symptoms appear. Amyotrophic lateral sclerosis is fairly rapidly progressive, and most patients die within 2 to 3 years. There are exceptions, and like others we have seen patients who survived 5 or 6 years, but in the very vast majority of cases the statement holds that we are dealing with a subacute and invariably fatal syndrome. It is worthy of comment that those patients with amyotrophic lateral sclerosis survive longest in whom the pyramidal tract signs predominate, particularly if the lower extremities are first or largely affected; while those die soonest in whom the atrophy predominates, especially in the cervical and bulbar regions. It would seem, therefore, that we are dealing with 3 different conditions of unknown etiology; that there is some selective affinity of the pathogenic agent for different structures in the 3 syndromes; that if the selectivity is limited either to the anterior horn cells and their nuclear homologues of the cerebral nerves or to the pyramidal pathways the result is a slowly progressive one; and that if by chance the old and new motor systems are simultaneously affected, the progress is rapid and the disease invariably fatal.

The conviction has gradually grown on us that amyotrophic lateral sclerosis is not one disease entity. It is true that the majority of cases are so-called typical or, as we should prefer to designate them, *primary;* but there are many which seem to us to be *symptomatic.* The first group appears to be the result of a "degenerative" process. There is some inferential evidence that deficiency plays a rôle in some cases of the primary group. The pathologic picture bears close resemblance to

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that seen in known deficiency diseases. The selectivity of involvement points in that direction. The isolated instances in which vitamins seem to play a rôle is another consideration. The relentless and uniformly progressive course is also suggestive. In any case the suspicion is very strong that the primary group represents one syndrome. On the other hand, there is no doubt, from our material and from numerous instances recorded by others, that inflammation of the nervous system can give rise to a syndrome of anterior horn and pyramidal tract disease. This is attested by clinical histories and by spinal fluid changes with increased cells and protein. The increase in protein alone is not altogether conclusive as one occasionally observes the rise in cases which appear to be primary. Third, there are few but definite instances of amyotrophic lateral sclerosis which are unquestionably the result of vascular disease. They are apt to be cases which begin with bulbar signs and symptoms, possibly also at first pseudobulbar, in whom the pyramidal tract signs though present are not very pronounced. They occur mainly in persons of advanced years. Finally, to these 3 syndromes one may possibly add a fourth consisting of 2 cases which followed spinal anesthesia. They may be designated as toxic, and there may be other instances, but the proof of toxic factors is otherwise lacking.

The statement has been made that the progress of fibrillations varies with the progress of the disease; that is, the more rapid and widespread the fibrillations the more rapidly fatal the disease. In our experience this is only partly true. We have seen instances where fibrillations ceased and the disease progressed rapidly nonetheless; others in whom fibrillations were comparatively rare throughout a fairly rapid course; still others which showed marked fibrillations with a protracted course. We have also observed marked atrophies with rare fibrillations and widespread fibrillations with moderate atrophies. One cannot therefore always assert the parallelism nor prognosticate the course of the illness from the fibrillations alone.

Of interest in our cases was the comparatively frequent onset with bulbar signs and symptoms. These, and pseudobulbar signs, generally come late, but the syndrome in several of our patients began with loss of voice, difficulty in speaking, facial paralysis, distressing sialorrhea, and the emotional disturbances seen in pseudobulbar palsy. All of the patients did badly. Not easily explained were the few cases with pain at the onset of the illness. While rare instances of amyotrophic lateral sclerosis with objective sensory signs are recorded in the literature, subjective sensory disturbances may be complained of. In our cases the pain generally ceased as the disease progressed. Whereas emotional disturbances were comparatively frequent, no patient in our series showed either minor or major psychotic disturbances.

Finally we would confirm what is fairly well known, the want of parallelism between hyperactive deep reflexes, the Babinski sign and absent abdominal reflexes. The first are invariably present and obviously point to pyramidal tract involvement; the last two are not always found but their absence is no evidence against involvement. The explanation for this is not clear.

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Conclusions. 1. We have recorded the clinical manifestations of 81 cases of amyotrophic lateral sclerosis, studied the clinical types, the various modes of onset, the unusual manifestations, possible precipitating factors, clinical variants, and the course of the disease. In general we would suggest the division of cases into *primary* and *symptomatic* groups.

2. It seems that amyotrophic lateral sclerosis is not one disease entity dependent upon one etiologic factor, but a syndrome of varying etiology. The largest group consists of so-called degenerative cases, some of which may possibly be the result of selective deficiency. Smaller groups may be the result of inflammatory processes or vascular changes. An even smaller group may possibly be toxic in nature.

3. From our own observations and those of others, the conclusion is justified that amyotrophic lateral sclerosis, progressive muscular atrophy and uncomplicated lateral sclerosis are three different entities. The first is comparatively rapidly progressive and invariably fatal, the other two are very chronic and last years and years.

4. While the intensity and extent of fibrillations often reflect the gravity of the disease there is no constant parallelism between them and one cannot prognosticate on the basis of fibrillations alone.

5. In many cases pseudobulbar manifestations may signalize the onset of amyotrophic lateral sclerosis.

6. Our studies confirm the want of parallelism between presence of active deep reflexes, absence of abdominal reflexes and a Babinski sign, despite involvement of the pyramidal tracts. The first always is present, the second two may or may not be.

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THE ELECTROCARDIOGRAPHIC CHANGES FOLLOWING ARTIFICIAL HYPERPYREXIA*

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Much speculation has existed regarding the significance of electrocardiographic (ECG) changes seen after artificially induced hyper-

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pyrexia. It is the purpose of this work (1) to describe ECG changes of a type not mentioned in the literature following hyperpyrexia, and (2) to attempt an explanation of them.

Vesell and Bierman,[12] in 1936, reported the detailed ECG changes in 10 patients subjected to artificial hyperpyrexia, and stated that the alterations of the individual waves were not uniform. They found that P and T waves were almost as frequently increased as decreased in size, and that the RT level usually was depressed, never elevated. They attached special significance to the development of a prominent Q-3 in one instance. They felt that the changes probably were due to "reflexes, tachycardia, local cardiac and general chemical and physiologic alterations." They concluded that none of the changes were permanent, and that it could not be inferred that fever produced any harmful effect upon the heart.

At the same time, Simpson[10] stated that the post-fever ECG showed only minor transient alterations. When questioned regarding the relationship of these changes to the degree of alkalosis, he replied that some degree of alkalosis was present uniformly in patients subjected to high, sustained, artificial fever.

Neymann,[9] in 1938, stated that the ECG showed increased rate, frequently with shortening of the PR interval. He added that the T wave usually was changed—frequently obliterated—and that the changes might last several days, but that fever has no permanent effect on the normal heart.

In 1941, Dawber[3] reported a case of "coronary thrombosis," following hyperthermy, in a 21 year old patient. The first ECG was taken 5 days after the acute attack of sharp substernal pain, accompanied by vomiting, and showed inverted T waves in leads II and III, and diphasic (beginning inversion) in lead I. Right axis deviation was present. There was no elevation of the S–T segments; if anything, there was a slight depression. There were no chest leads taken, and there was no record of the erythrocyte sedimentation rate or of the white cell count. The patient's temperature was not mentioned. A second tracing taken 13 days later (again without chest leads) showed inversion of T-1 with an upright T wave in leads II and III. Tracings taken approximately 2 and 4 weeks later showed no significant changes. A final tracing, taken 4 months after the first one, was normal. This was the only tracing in which a chest lead was taken. At this time (4 months after attack) the sedimentation rate was 2 mm. and the white cell count was 8600 with a normal differential count.

During the same year, Knies[6] reported the ECG changes observed during 52 treatments of 20 patients. He found the changes to be insignificant with none suggestive of cardiac damage. He agreed in general with the observations of Vesell and Bierman, and concluded that the changes were the result of physiologic processes incidental to the temperature increase regardless of its mode of induction.

In 1943, Turville and Fetter[11] reported on the ECG changes following artificial fever in 13 patients. They were unable to correlate the changes with the age of the patient, the height of the fever, or the

cardiac rate. Their observed changes apparently were similar to those previously reported, but they felt that the changes were more significant and should call for closer watching of the patient with termination of the fever at the earliest sign of cardiovascular failure.*

Procedure. All fevers were induced by means of a cabinet employing the principle of hot air whose relative humidity ranges from 85 to 95%.

Each patient received a *conditioning fever* during which the body temperature was elevated to 101° F. for 30 minutes. Such fever was administered to acquaint the patient with the technique of the forthcoming therapeutic fever, and to give him the benefit of increased blood volume, which is said to result from this procedure.[7] In the administration of *therapeutic fevers*, an attempt was made to maintain the patient at between 105° to 107° F. for a period of 5 to 10 hours. These objectives were not attained in all cases, patients being removed from the cabinet for various reasons.

In an attempt to maintain normal physiologic relationships at the elevated temperature, all patients received fluids up to 500 cc. per hour, continuous oxygen, and, when necessary, 50% dextrose.

Electrocardiograms were taken routinely on all patients before and after fever therapy to determine the effect, if any, of this procedure. Tracings also were taken following conditioning fevers, since these offered an opportunity to study the effect of fevers differing in duration and intensity.

In several instances, tracings were taken at regular intervals throughout the fever, but this was discontinued because it seriously interfered with the treatment. It is necessary to maintain a high degree of humidity in the fever cabinet, and this can not be done if the cabinet is frequently opened. Furthermore, this work already had been performed and reported by Knies,[6] and a repetition seemed unnecessary.

The series of 86 patients, with a total of 118 sessions of fever.† Of these, 80 were therapeutic fevers, and 38 conditioning. In the case of the therapeutic fevers, the height and duration are given with the data.

The data are found in Table 1. Briefly, it was found that of the 80 cardiograms following therapeutic fever, 64 showed changes of an insignificant nature, 7 showed significant changes, and 9 showed no change whatever from the pre-fever tracing.‡ Of the tracings taken following conditioning fever, 21 showed no change, 16 showed insignificant changes, and none showed changes of any significance.

Insignificant Electrocardiographic Changes. *Character.* Previous workers[12] have described in detail§ the post-fever changes in the individual components of the ECG. It was desired to check these findings. Consequently, a series of 27 cases of those showing insignificant changes was charted and analyzed in detail. The result of this analysis is in Table 2.

* While I am in full agreement with the conclusion that patients should be removed from the fever cabinet at the earliest sign of cardiovascular failure, I fail to see any direct relationship between this condition and the ECG changes as described.

† In the case of multiple therapeutic fevers in a single patient, only the first was included for statistical purposes except in a few cases where the other sessions produced ECG changes of different significance.

‡ Although 7 cases are listed as showing significant changes, it will be seen that 9 are discussed. This is because one (5177) showed insignificant changes in his post-fever tracing, developing significant changes on the following day. The other (6673) was studied just prior to publication and was not listed.

§ It is felt that the work of Vesell and Bierman, in which amplitude is measured down to 0.1 mm. and time down to 0.01 sec., attempts to obtain an unwarranted degree of accuracy.

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TABLE 1.—DATA REGARDING CASES UNDERGOING HYPERPYREXIA

No.	Age	ECG	Rate	CO_2	Liver	Fever: Time (hrs.)	Fever: Degree	Vomit	Psyche	Shock	Short fever: Rate	Short fever: ECG	Remarks
5801	20	3	60–110	..	..	8	106.8						
5128	19	n	85–110	44–36	..	10	106.8						
5413	26	3	85–115	..	..	4½	106.8	..	..	..	85–110	1	
4950	28	n	75–135	..	..	8	106.5	v	..	..	..	..	Plus 2 changes 4 hr. post-fever; rate then 83.
5176	21	1	75–115	52	..	5	106.8						
5355	24	2	65–100	40	..	10	106.8	v	DN	..	65–80	2	
4941	20	2	65–110	..	..	8	106.5	..	..	..	..	..	Normal 2 hr. post-fever; rate 91.
5079	20	2	90–110	46	..	8	106.8	..	..	..	90–90	n	
4743	42	n	100–105	..	..	2	103.3	..	..	..	100–115	n	Removed—fast pulse, low b.p.
5205	22	1	65–85	54–46	SCJ	8	106.8	v	D	..	65–100	n	
5888	25	2	80–110	..	..	8	106.8	..	..	..	..	..	P-2 sharp, T-4 flat; normal in 3 days.
5318	31	s	70–90	51–40	..	6	106.8	..	..	S	70–83	n	Stopped: b.p. 90/60; inverted T-4.
5139	19	n	60–100	56–54	..	8¼	106.8	..	D				
5077	20	n	70–95	42	SCJ	10	106.8	..	..	..	70–88	n	
4954	27	1	70–110	..	J	10	106.8	..	D	..	70–92	1	
5238	26	1	75–115	..	..	6½	106.8	..	..	S	75–83	n	
5081	25	2	75–110	..	J	9	106.8	..	T	SPR	75–85	n	
5085	24	1	60–130	..	..	¼	106.8	..	..	..	60–94	n	Stormy 2 hr. induction; cyanotic; restless; tachycardia.
5865	21	1	70–110	..	..	5½	106.8						
4385	23	2	55–110	..	..	5	105.0	..	..	..	..	..	Sl. elevation of ST-2 and 3; 4 hr. post-fever.
5193	24	..	..	..	..	..	..	..	..	..	75–110	2	
5148	20	2	85–115	46	..	9½	106.8	..	..	SPR			
5175	28	1	85–100	50–36	..	9	106.8	..	..	PR	85–80	n	
4907	25	4	75–110	..	..	8	106.5	v	..	..	..	..	1 week later, ST-T normal, but P waves entirely changed.
5166	19	n	65–110	..	..	5½	106.8	v	..	S	65–90	n	
5785	19	1	70–110	43	SCJ	9½	106.8	v	..	..	70–90	n	
4742	40	1	80–125	..	..	10	106.8	v	D	..	80–112	1	
5135	29	..	..	..	..	..	..	..	..	..	90–85	n	
5317	23	2	85–125	57–42	SCJ	7½	106.8	..	..	..	80–105	n	
5082	35	2	85–115	..	..	10	106.8	..	..	..	85–90	n	
5281	49	2	75–105	..	..	1½	105.0						
5102	23	2	85–145	46–40	..	5	106.8	v	..	..	85–108	1	
5968	23	3	100–125	..	..	5	106.8	..	..	..	100–108	n	
5057	25	n	80–95	..	SCJ	10	106.8						
5083	25	4	70–90	..	SCJ	10	106.8	..	..	..	70–90	n	
4939	23	1	90–105	..	..	4½	106.8	v	D				
5055	26	1	100–100	52	J	9	106.8	v					
5771	35	2	75–105	..	..	5	106.8	..	..	..	75–83	n	Slight cyanosis.
5236	19	2	80–125	61–44	SCJ	4½	106.8	..	TD				
5127	20	1	60–110	56–38	SCJ	10	106.8	..	D	..	60–92	n	
5087	27	2	60–115	44	J	10	106.8	..	..	..	60–73	n	
5030	28	2	65–105	..	J	12	106.8	..	..	..	65–112	n	Slight cyanosis.
5174	25	1	75–100	53–36	..	8¼	106.8						
5129	29	2	70–105	50	..	5½	106.8	..	..	S	70–83	1	
5461	25	s	75–95	..	..	1½	106.8	..	D	..	75–85	2	T-1 inverted; T-4 diphasic; ST-2-3 depressed; 3 weeks later, normal.
5029	19	..	..	..	..	..	..	..	..	..	70–90	1	
5354	19	2	65–115	..	..	10	106.8	..	..	..	65–80	1	
5864	23	4	80–95	..	..	5	106.8						
5936	23												

5030	28	2	85–105	44	3	10	106.8	..	..	..	80–72	n	Shift to right axis deviation.
5174	25	1	75–100	53–36	..	8½	106.8						
5129	29	2	70–105	50	..	5½	106.8	..	..	S	70–83	1	
5461	25	s	75–95	..	..	1¼	106.8	..	D	..	75–85	2	T-1 inverted; T-4 diphasic; ST-2-3 depressed; 3 weeks later, normal.
5029	19	..	..	..	..	..	..	..	..	..	70–90	1	
5354	19	2	65–115	..	..	10	106.8	..	..	..	65–80	1	
5864	23	4	80–95	..	..	5	106.8						
5936	23	..	..	..	..	..	..	..	..	..	95–95	n	
5835	23	1	60–100	..	..	3¼	106.8						
5319	27	..	..	..	..	..	..	..	..	..	100–105	2	
5280	22	2	85–110	..	..	5	105.0	..	..	..	..	..	This pt. had 4 similar post-fever tracings, 4 fevers.
5140	19	3	75–110	48–32	..	3½	106.8	..	A	S	75–117	2	
5310	31	2	65–126	..	..	6	106.8	..	T				
5177	28	2	70–110	38	..	8	106.8	..	..	SPR	..	..	Myocardial infarction next day.
5883	23	s	70–105	..	..	10	106.8	..	..	..	70–92	3	ECG of myocardial infarction.
5880	22	s	75–100	..	..	6	106.8	..	..	..	75–83	n	T-2 and 3 inverted; T-4 diphasic; normal after 2 days.
5881	22	s	60–100	..	..	1½	106.8	..	..	..	60–60	n	T-2 and 3 inverted; later, normal.
5956	22	s	85–100	..	..	8	106.8	..	..	..	..	..	Inverted T-4.
6046	32	s	80–115	..	..	8	106.8	..	..	..	..	..	Inverted T-4; depressed ST in limb leads; normal in 2 days.
5938	25	4	65–100	..	..	5½	106.8						
5857	29	3	70–85	..	..	8	106.8						
6047	28	2	95–110	..	..	7	106.8						
5886	25	2	80–110	..	..	8	106.8						
6093	20	2	80–120	..	..	2	106.0	..	..	..	..	..	Fatigue
5866	23	2	90–100	..	..	1½	106.2	..	..	..	..	..	Cyanotic; restless; confused.
6031	18	2	70–95	..	..	5	106.5	..	..	..	..	..	Fever discontinued, low b.p.
5826	28	2	70–100	..	..	8	106.2						
5980	22	4	65–95	..	..	8	106.8						
6034	27	2	80–110	..	..	8	106.8	..	..	..	..	..	Precordial pain; serial ECG normal.
6033	21	n	80–75	..	..	3	106.5	..	..	..	..	..	Treatment discontinued—fast pulse.
5979	31	1	90–110	..	..	2¼	106.5	..	..	..	..	..	Pulse 160 to 180.
6183	20	n	75–75	..	..	6	106.2	..	D	..	..	..	Restless and disoriented.
5863	29	4	75–110	..	..	1½	106.8	..	H				
5858	22	2	70–90	..	..	4	106.8						
6194	21	3	80–110	..	..	5	106.2	..	..	..	80–95	2	Drop in blood pressure.
5887	19	2	55–75	..	..	2½	106.5						
6142	24	4	80–100	..	..	6½	106.5	..	..	..	..	..	Cyanosis; vertigo; restlessness; fatigue.
6097	23	2	85–100	..	..	5¼	106.2	..	..	..	..	..	Profound fatigue; drop in b.p.
5991	19	2	75–115	..	..	6	106.2	..	..	..	..	..	Fatigue; pain in abdomen.
6382	25	3	50–90	..	..	1	106.2						
6141	21	2	65–105	..	..	8	106.2						
6390	23	3	55–120	..	..	2	106.2						
6080	25	..	..	..	..	..	..	..	..	..	60–80	n	
6025	22	2	83–105	..	..	5	106.8						

n—no change
s—significant change
1—slight lowering of T waves
2—moderate lowering of T waves
3—marked lowering of T waves
T—tetany
D—delirium or excitement
H—hysteria
A—amnesia
V—vertigo of 24 hrs. durationS
N—nystagmus
J—jaundice
CJ—subclinical jaundice
PR—plasma reaction
v—bloody vomitus

It may be stated, in general, that about one-half of the cases showed increased amplitude of the P wave, with a maximum increase of 1 mm. There were very few cases in which the P wave was decreased in amplitude. In the majority of cases, there was some diminution of the voltage of the QRS complex, but this never exceeded 1 mm. in the limb leads. The S–T segment was depressed in but 10 of the cases (Vesell and Bierman[12] found the R–T phase depressed in "almost every case") and was elevated in none. The majority showed T waves whose amplitude was decreased as much as 4 mm. in the limb leads, but in several cases the amplitude was increased.

TABLE 2.—DATA REGARDING ELECTROCARDIOGRAPHIC CHANGES IN 70 TRACINGS TAKEN DURING 43 FEVER SESSIONS

Number of patients, 27; number of fever sessions, 43; number of electrocardiograms, 70

	No change	Increase	Maximum increase (mm.)		Maximum decrease (mm.)
P wave*	18	20	1	4	1
R wave	11	9	5†	26	5†
S–T segment	33	0	0	10	1
T wave	13	4	1‡	26	4
Bazett's "K"	1	33	0.096§	9	0.065§

* One case questionable, as P wave was superimposed on T wave of preceding complex.

† In lead IV-F, the maximum increase was 20 mm. and the maximum decrease was 9 mm.

‡ Maximum increase of 5 mm. in lead IV-F.

§ Average increase 0.037; average decrease 0.021.

The one measurement apparently disregarded by previous workers was the Q–T interval. This is the measurement of the electrical systole and is correlated with the square root of the cycle length. The value obtained by means of this correlation is known as Bazett's "K."* This value was unchanged in 1 case, was decreased in 9, but was increased in 33. Furthermore, it is seen that the average increase was 0.037 while the average decrease was but 0.021. This points toward this figure as being one of the most constant changes yet described in the ECG following artificial fever. Moreover, this change cannot be ascribed to the rate, as this factor already has been accounted for in the formula.

It must be reëmphasized that none of the changes described are specific following fever therapy; that none are constant in the degree or direction of the change; and that, generally speaking, they are of no significance.

Classification. Broadly speaking, the ECG changes following fever therapy fall into 3 groups showing: (1) No change; (2) no significant change; and (3) significant change. In the section dealing with the insignificant changes, it was shown that these changes were not constant in direction and amplitude. For statistical purposes, it is necessary to devise a more simple classification of these changes rather than to list separately the effects upon each complex.

$$* \text{ Bazett's "K"} = \frac{\text{Systole}}{\sqrt{\text{Length of cycle}}}$$

The following gradation was found to be satisfactory: N—no change; 1—slight lowering of voltage of T waves in leads I, II, or IV; 2—moderate lowering of voltage of T waves in leads I, II, or IV; 3—marked lowering of voltage of T waves in leads I, II, or IV; 4—1, 2, or 3, with depression of the ST segment; S—significant change.

In this scheme, any inversion of the T wave, except in lead III alone, was considered to be abnormal and was not classed in the insignificant changes.

It should be remembered that grades 1 to 4 consist of *insignificant* changes and that the grouping is merely a means of convenience rather than an attempt to reach unwarranted conclusions.

Jaundice. ECG changes in gall bladder disease have been described.[4] It is possible that these changes are due to an abnormal amount of bile salts in the blood stream. Knowing that jaundice can be a complication of hyperthermia, it was desired to determine if this was a factor in the production of the ECG changes following fever.

Those patients showing hepatic involvement were divided into two general classes: (1) jaundice; and (2) subclinical jaundice, which consisted of those with increased serum bilirubin in amount insufficient to cause clinical jaundice.

The data in Table 1 show that of the 5 patients with jaundice, none showed greater than grade 2 insignificant changes in the cardiogram. It is of interest that Patient 5055 had severe hepatic damage, yet his cardiogram showed only grade 1 insignificant changes.

Of the 8 patients with subclinical jaundice, 2 showed no change, 1 showed grade 4 changes, the remainder varying between grades 1 and 2. None showed changes of any significance.

These data show that liver damage, as indicated by increased serum bilirubin, was not a factor in the production of the ECG changes following fever therapy in this series of cases.

Alkali Reserve. Simpson[10] stated that some degree of alkalosis was present uniformly in patients subjected to high, sustained, artificial fever. Barker[1] inferred that this might be a factor in the production of ECG changes.

In 11 cases, the carbon dioxide combining-power was determined as a routine measure before and after fever therapy (Table 1). In every case this value was lowered. Of these, 2 cases showed no changes in the cardiogram, and 1 showed significant changes. Of the remaining 8, 4 showed grade 1, 3 grade 2, and 1 grade 3 changes.

In 10 cases, a post-fever carbon dioxide combining-power was determined because it was felt that there might be some derangement of the alkali reserve. In each instance, the result either was normal or indicated a diminution of the alkali reserve, the values ranging from 52 to 38 volumes %. The cardiographic changes ranged from none to grade 2.

While these data do not indicate the presence of acidosis, they do show that alkalosis was not a causative factor of the cardiographic changes in this series of cases.

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The Effect of Rate and Fever. STATISTICAL STUDY* *Rate.* With little or no change in rate, the possibility of there being no ECG change is great. With changes between 10 and 20 beats per minute, the possibility is more than 2 to 1 of there being changes, and when the increase is more than 20 beats per minute, the odds are overwhelming in favor of there being changes.

Fever. In the case of conditioning fevers, one may or may not find changes; the possibility of there being no change being slightly greater. In all of the therapeutic fevers, however, changes are almost always present.

These findings support the previously expressed opinion that increased cardiac rate is a major, but not the sole, factor in the production of the ECG changes following fever.

Significant ECG Changes. The following cases were admitted to the hospital for the purpose of receiving hyperpyrexia. All had drug-resistant gonorrheal urethritis except Case 5318, who had gonorrheal arthritis. Each had a cardiac examination, including ECG, prior to fever. None showed any abnormality.

CASE 5177 (Fig. 1). This 28 year old patient gave a history of rheumatic fever. On April 27, he received 8 hours of therapeutic fever at 106.8° F. Although fatigued, his general condition was said to be good. His blood pressure was 106/70, and his post-fever ECG showed only insignificant changes. Several hours later his blood pressure fell to 86/60. At about 2 A.M. on April 28, following 250 cc. of a plasma infusion, he developed fever and chill. The chill lasted about 15 minutes, and the blood pressure was 102/80. At 7 A.M., the blood pressure was 80/60, and at 11 A.M., the patient complained of severe substernal burning and pressure. At 2 P.M., the blood pressure was 98/70, the heart sounds were distant, and the ECG showed marked elevation of ST-4.† On April 29, his blood pressure was 100/70, and he was comfortable while receiving accepted treatment for myocardial infarction. His white cell count was 11,250 with 92% polys and his sedimentation rate was 19 mm. In the morning of the same day his ECG showed a marked return to normal, but by evening, the S–T segment was abnormally elevated in lead CR-6. For the next few days, his clinical condition was essentially unchanged; the blood pressure ranging between 100/80 and 120/60. Examination of the ocular fundi revealed no evidence of old or recent hemorrhage. On May 9, the patient complained of precordial pain, a diastolic murmur was heard over the aortic area, a third sound was heard over the apex, and a Roentgen ray revealed enlargement of the left ventricle. The ECG, which in the meantime had shown inverted T waves in the limb leads and gradual regression of the inverted T in CR-6, showed marked inversion of the T wave in IV-F, CR-4, and CR-6. His white cell count was 7400 with a normal differential, but his sedimentation rate remained elevated at 17 mm. On May 22 a Roentgen ray showed decrease in the size of the left ventricle, and there were no murmurs present. Because of this, and the fact that no murmurs have been heard since, it is felt that the findings of May 9 were due to dilatation of the left ventricle. From this date on, improvement was gradual but progressive. By early July, his ECG and sedimentation rate had returned to normal.

It is obvious that this patient suffered severe myocardial damage, the cause of which is questionable.

* These results are based on the data of the entire series of cases. "Significant" changes are included for completeness only, it being realized that this group is entirely too small for the purpose of statistical comparison.

† Throughout this paper, "ST-4" and "T-4" refer to complexes in lead IV-F.

It is well known that hyperpyrexia is capable of causing multiple small hemorrhages in various organs.[5,8] With the marked elevation of ST-4, seen in the ECG of April 28, it was felt that the underlying pathology might be a small subepicardial hemorrhage. While this cannot be ruled out, the course of subsequent events makes it improbable.

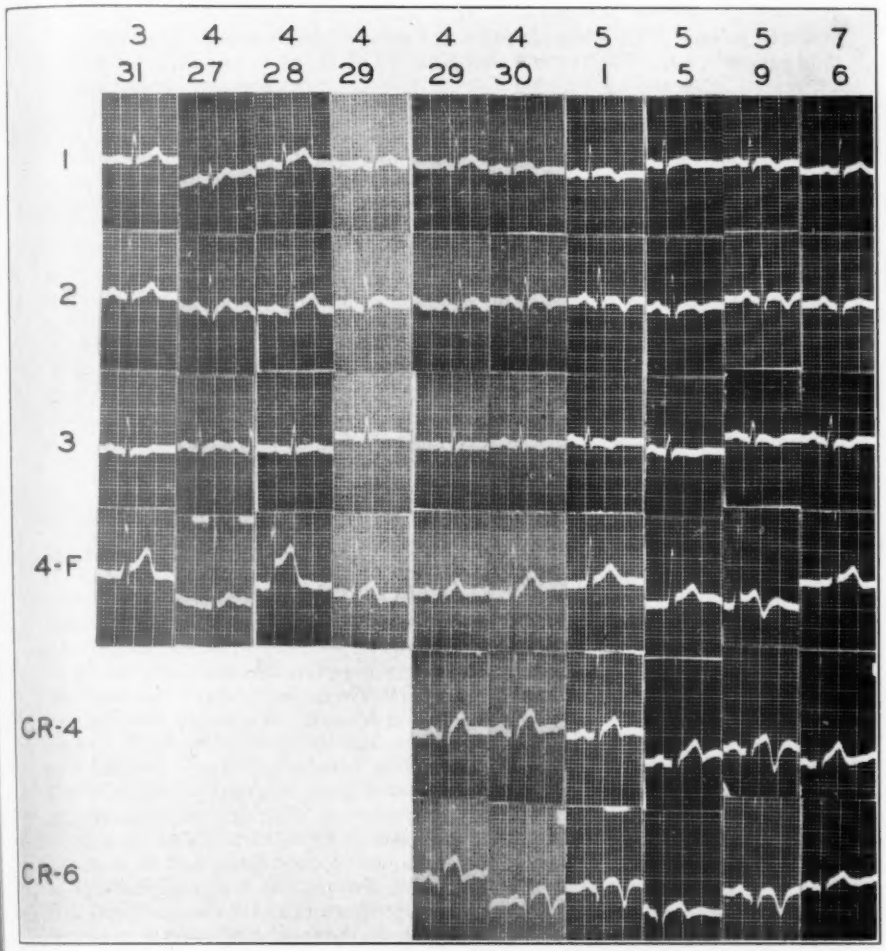

FIG. 1.—Electrocardiograms of Case 5177, showing acute change on April 28 with progression up to May 1; some return toward normal by May 5; and acute recurrence of changes on May 9.

Despite the fact that the T waves in the limb leads and the ST-4 suggest epicardial, rather than myocardial, involvement, study of the entire series of tracings is more indicative of coronary thrombosis, because of the sudden change seen in the tracing of May 9. Had the original condition been due to hemorrhage, one would expect the ECG

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gradually to return to normal. In coronary thrombosis, however, it is not infrequent to have an extension of the thrombus, causing changes similar to these. Furthermore, it would be unusual to find the hemorrhage following fever involving a single organ. In this case there was no evidence of hemorrhage at any place in the body. Also, blood taken from the patient's arm on April 28 coagulated immediately.

Case 5956. This 22 year old patient received 8 hours of therapeutic fever at 106.8° F. during the night of May 29–30, and apparently reacted in a normal manner. Following fever he had no complaints except headache and mild lumbar pain. The routine post-fever ECG showed low voltage T waves in the limb leads and an inverted T-4. His blood pressure stayed in the vicinity of 100/65, and the sedimentation rate was 2 mm. The white cell count was 6400 with a normal differential. On May 31, the tracing showed limb leads which were less abnormal and T-4 which was less inverted than previously. The CR leads were normal but ST-4 was elevated. The blood pressure averaged 95/60. On June 1, T-4 was entirely upright, but showed slight notching of its descending limb.

Subsequent course showed gradual return of the blood pressure and ECG to normal. The patient's temperature and white cell count were normal throughout the entire illness. The sedimentation rate was 2 mm. on June 14, but rose to 15 mm. on June 21. The patient was asymptomatic except for headache, and was about to be discharged from the hospital when, on July 8, 39 days after fever therapy, he developed, for the first time, precordial pain. This was accompanied by an elevation of ST-4 with inversion of T-4, a white cell count of 5300, and a sedimentation rate of 16 mm. The pain was relieved by oxygen. On July 9, the ECG was normal except for notching of T-4. His course from there on showed gradual improvement.

Because of this change that occurred on July 8, it is felt that this also is a case of myocardial infarction, probably on the basis of thrombosis of a small branch of a coronary artery.

Case 5883. This 23 year old patient had rheumatic fever at age 15 with frequent recurrences since. He had no symptoms at any time referable to the cardiovascular system, and his pre-fever examination was normal. An ECG was normal, although the R wave in lead IV-F was only 2 mm. He received 10 hours of therapeutic fever at 106.8° F. on May 19. Following this, he was moderately fatigued, and his blood pressure was 100/60-0. The heart sounds were distant but there was no evidence of pericardial effusion. Twenty-five minutes after removal from cabinet, he complained of sharp pain in the left lower chest. This pain was relieved by eructation of a large amount of gas. His ECG showed lower voltage and diphasic T-4. About 3 hours later, his blood pressure was 100/40, he again complained of chest pain, and he vomited 300 cc. of light brown fluid. At midnight, the patient was complaining of dyspnea. Throughout the night his blood pressure ranged between 80/50 and 95/55. On May 20, his ECG showed definite cove-shaped inversion of the T waves in leads IV-F, CR-2 and CR-4. The patient was comfortable except for a dull, squeezing, precordial pain which did not radiate. The blood pressure was 96/60, the white cell count was 8850 with normal differential, and the sedimentation rate was 3 mm. His condition remained unchanged throughout the day, and his pain was relieved by oxygen and morphine. On the morning of May 21, he complained of several attacks during the night when his oxygen mask had slipped off, but his general condition remained the same. On May 22, he still complained of dyspnea and precordial pain, but the heart sounds were of better quality, and the blood pressure was 100/60. His ECG showed return toward normal. The T waves, which had been inverted, were now diphasic. His condition showed gradual but definite improvement. Subse-

quent white cell count and sedimentation rate were normal, and the ECG approximated the pre-fever normal on July 6.

On July 15, 56 days following fever therapy, while gradually increasing his physical activity prior to discharge from the hospital, he again developed precordial pain. His ECG on the following day showed slight elevation of ST-4, with inverted T-4. The T wave in lead CR-2 also was inverted. The patient was afebrile and his white cell count and erythrocyte sedimentation rate were normal. His symptoms subsided while he was kept at absolute bed rest. On July 19, the ECG again had returned to its pre-fever normal.

From this point on, improvement was gradual but definite.

The sudden change on July 18, as in Case 5956, leads to the conclusion that the entire syndrome was due to occlusion of a small coronary artery.

Case 5318. This 31 year old patient was given 6 hours of therapeutic fever at 106.8° F. on April 5. This treatment was discontinued because the blood pressure fell, and stayed at 90/60 and below. The post-fever tracing showed inversion of the T wave in lead IV-F with a QRS complex of entirely different configuration. A tracing taken several days later was similar to that taken prior to the fever.

On April 30, he received a 5-hour fever to which he responded well. There were no obvious complications, and no ECG was taken.

On May 26, he received 3 hours at 106.5° F. This treatment was discontinued because of cardiovascular depression with blood pressure readings of 86/60 and 90/60. He was given plasma which caused a reaction. An ECG again showed inverted T wave in lead IV-F.

Despite the fact that the QRS complexes in lead IV-F differed in contour from time to time in the different tracings, it can be stated positively that the electrode was placed near enough to the same position to make them comparable.

Throughout the entire course of hospitalization, the patient never complained of precordial pain. He had a total of 13 white cell counts, all of which were normal. His sedimentation rate was 26 mm. on May 24, and 24 mm. on June 11.

Case 6046 (Fig. 2). This 32 year old patient received an 8-hour therapeutic fever at 106.8° F. on May 29. At one time during the fever, his remarks were irrational, and at the end of the fever he was fatigued, but his general condition was said to be good. Following fever, he had no complaints, and his blood pressure stayed at about 120/80; but his ECG showed flattening of all T waves, depression of ST-2, and inversion of T-4. On May 31, his tracing had returned to normal.

His white cell count was normal on several occasions, and his sedimentation rate on June 1 was 2 mm.

Case 5461. This 25 year old patient had no abnormal physical signs except for a soft, grade 1, systolic murmur at the apex; in all probability a functional murmur. Therapeutic fever was attempted on May 13, but discontinued after 1 hour at 106.8° F. because the patient became hysterical and attempted to break out of the cabinet. His blood pressure remained perfectly normal, and he had no symptoms referable to the cardiovascular system. His post-fever ECG showed inversion of T-1, diphasic T-4, and low voltage T waves with depressed ST segments in leads II and III. A tracing taken on May 17 showed return to normal except for slight elevation of ST-4 and absent S-4. On June 7, a tracing was entirely normal.

Case 6673. This 24 year old patient received an 8-hour therapeutic fever at 106.2° F. on June 26. There were no complications, and his condition following fever was considered to be excellent. There were no cardiac symptoms at any time, and his blood pressure remained in the vicinity of 110/80 during and following the fever. His post-fever ECG showed inverted T waves

with depressed ST segments in leads II and III, with a small diphasic T-1, and notched T-4. A tracing taken June 30 showed complete return to normal.

Several weeks later, following supervised exercise, his ECG showed tachycardia with depression of ST in leads II and III and lowering of voltage, but no inversion, of the T waves.

CASE 5880. This 22 year old patient received 6 hours of therapeutic fever at 106.8° F. on May 20. His post-fever ECG showed inverted T waves in leads II and III. The patient had no complaints, and his blood pressure remained at about 110/80. On two occasions followed fever, his white cell count and differential were normal. His ECG was normal on May 22.

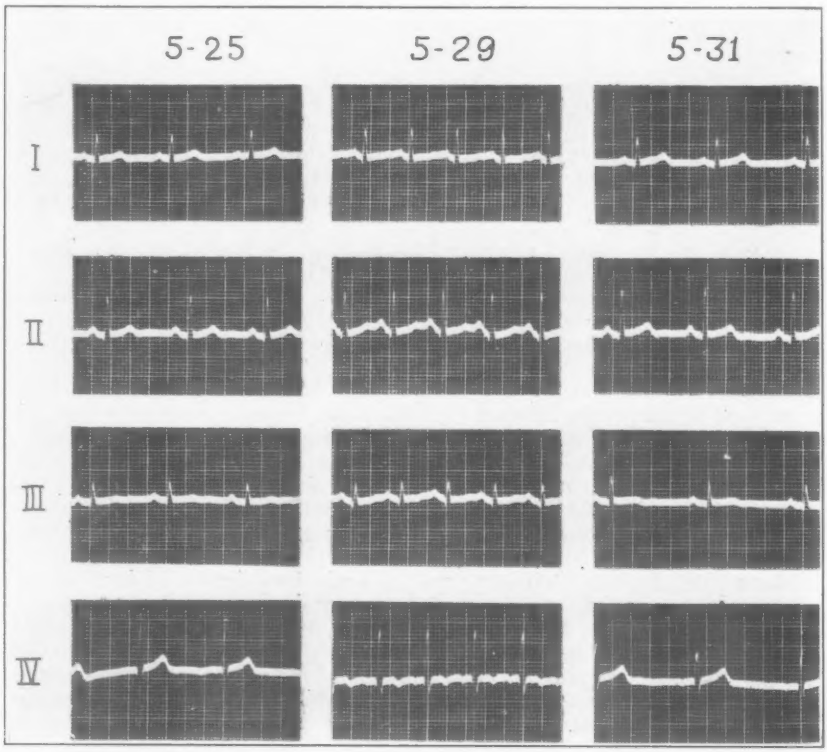

FIG. 2.—Electrocardiograms of Case 6046 showing typical "significant" post-fever changes.

Several weeks following fever, the patient was given supervised exercise, tracings being taken after light and moderate exertion. Tachycardia was the only change in the ECG.

CASE 5881 (Fig. 3). This 22 year old patient was given fever therapy on May 21. During induction of fever, he complained of weakness. Because of cyanosis and a blood pressure of 95/50, treatment was terminated after 1 hour and 20 minutes. At that time he complained of a severe pain in the right renal region, and an ECG showed the T waves to be small and inverted in leads II and III, while in the same leads the P waves were large and pointed. A tracing taken 1 hour later showed T-2 to be small but upright; the P waves remaining unchanged. Lead CR-2 (not shown) showed an unusually tall T wave. The patient's blood pressure rose to 110/75, and stayed at about this level. A tracing taken the following day was normal except for the large

T wave in CR-2. Tracings were retaken several times, and this finding remained constant. Therefore, it was felt to be normal for the individual. On two occasions following fever, his white cell count and differential were normal.

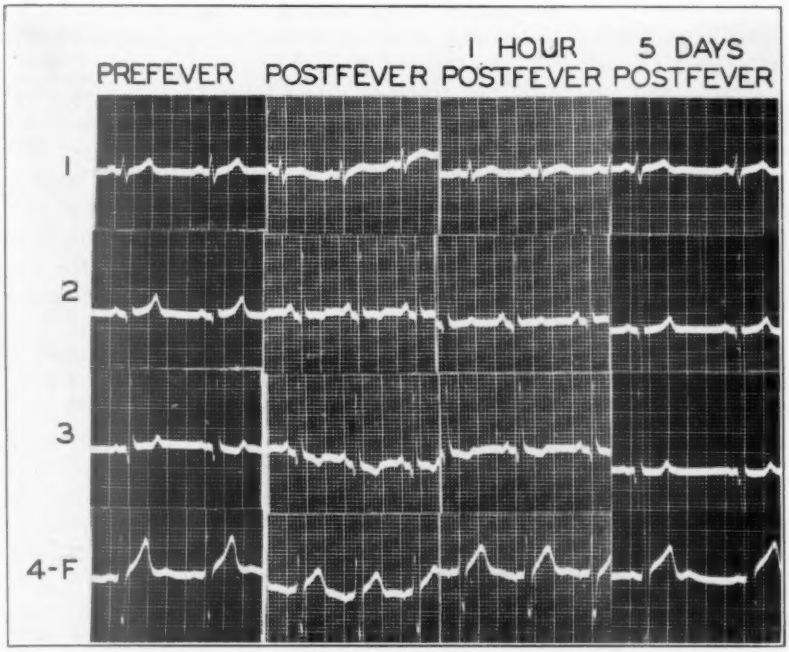

FIG. 3.—Electrocardiograms of Case 5881, showing definite change between the tracing taken immediately following fever and one taken 1 hour later. The CR leads were omitted from the illustration as they showed no change. *A*, Relationship of increase of rate to ECG changes. *B*, Relationship of fever to ECG changes. *C*, Correlation of amount of fever with the degree of change in rate.

Discussion. Cases 5177, 5956, and 5883 obviously had myocardial damage, probably on the basis of small coronary artery occlusions. While the possibility of myocardial infarction without coronary occlusion was considered, it was felt that such would not account for the relapse which occurred in 2 of the cases.

While Cases 5956 and 5883, prior to their relapse, show series of tracings comparable to those presented by some authors[2] as being due to tachycardia rather than myocardial damage, it is felt that the burden of proof rests with the person who claims that changes of this magnitude and duration are not due to myocardial damage.

Although 2 of the above cases (5177 and 5883) had definite rheumatic histories, their pre-fever examinations and cardiograms were normal. There is no evidence to show that the subsequent course was related to the rheumatic fever.

In the remaining cases, ECG changes were transient, there were no objective signs or subjective symptoms referable to the heart, and the laboratory work was entirely normal. Because of this, it is highly probable that the ECG changes were not on the basis of myocardial

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damage, but rather were due to a temporary myocardial anoxia, possibly of a relative nature due to the tachycardia. Most cardiologists have seen inverted T waves following paroxysms of tachycardia. These inverted T waves, however, *rapidly* return to their normal upright position. It is probable that the cases in this group showing temporary changes fall into this category.

Cases 5880 and 6673 had tracings taken following exercise. Case 5880 showed no change but tachycardia, while Case 6673 showed depression of the S–T segments. The fact that the post-fever ECG changes were not reproduced in these patients, following exercise, does not rule out increased rate as a factor. The added factor of duration of the tachycardia undoubtedly plays a rôle. Were it possible to exercise a patient for the same length of time as that spent in the fever cabinet, changes similar to those found in post-fever tracings might be obtained.

Summary. 1. In a series of 118 electrocardiograms (ECG) taken immediately after fever therapy, the changes from the pre-fever tracings are tabulated. Of 80 tracings taken following therapeutic fever, 64 showed insignificant changes, 7 showed significant changes, and 9 showed no change whatever from the pre-fever tracing.

2. The results published by previous workers who claimed that the S–T segment was almost always depressed following fever are not confirmed. It was found that there was a slight increase or decrease in the amplitude of the P waves and the QRS complexes and that the S–T segment was depressed in a few cases. The most constant change observed was an increase in the value of Bazett's "K," an index of the duration of electrical systole.

3. The effects of jaundice, acid-base balance, and cardiac rate on the post-fever ECG are discussed.

4. Three cases with myocardial damage following fever therapy are presented.

5. Of these 3 cases, 2 apparently were almost completely recovered when each suffered a relapse, 39 and 56 days, respectively, following fever.

6. Six cases that showed transient and significant ECG changes, following fever, are presented. The possible causes of these changes are discussed.

Conclusions. While the majority of ECG changes following fever therapy are insignificant and probably due to the effect of tachycardia, it is possible to have changes due to severe myocardial damage, such as that caused by occlusion of a small coronary artery.

In those cases with myocardial damage due to fever, one should not give a good prognosis merely because the patient is young and the causative agent (fever) has been removed. The treatment of these cases should be the same as that given myocardial infarction due to any other cause.

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CONCENTRATED RED CELL TRANSFUSIONS

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In recent years, with the establishment of many large blood banks, great quantities of plasma have been made and used, and as a by-product the settled erythrocytes were being discarded as a waste material. Generally, in the past, it has been little recognized that these concentrated red cells can be of definite therapeutic value, and in certain instances may even possess an advantage over the use of whole blood transfusions. More recently, however, interest in concentrated red cell preparations has become evident.

As early as 1918 Robertson[10] described a technique for the administration of red cells to humans, and in 1937 Castellanos and Riera[4] reported the successful use of red cells. In England there have been reports of the use of erythrocyte transfusions by McQuaide and Mollison (1940),[8] Williams and Davie (1941),[16] Vaughn (1941),[11] Whitby (1941),[13] and Watson (1943).[12] In 1942 Bagdasarov[2] mentioned their use in Russia. More recently, in this country, Alt,[1] Evans,[5] and Murray *et al.*[9] have reported on successful series of transfusions of concentrated red cells.

The object of this report is to call attention to the use of concentrated red cell transfusions; to demonstrate that they are as efficacious as whole blood in raising the hemoglobin level; that no deleterious effects result from their administration; and in certain instances that they possess an advantage over whole blood.

Procedure. The concentrated red cell preparations were obtained from regular hospital donors. The Fenwal apparatus, a semi-closed system, was used to collect 500 cc. of blood in 50 cc. of 5% sodium citrate solution. The blood was typed by the open slide microscopic method and then stored at 4° to 6° C.

The red cells were usually prepared for use as the occasion arose for them, for it is our impression that the life of the cells is decreased when they remain in the concentrated state too long. Whenever obtainable, the blood of the patient's own group was used; otherwise group O blood was used. The blood selected was from 2 to 7 days old, in accordance with the findings and recommendations of Wiener and Schaefer[14] and Belk and Barnes.[3] Before preparation the donor's blood was cross-matched with that of the recipient by the test tube method of Landsteiner.[15] If blood of more than one donor was to be

used in a transfusion, each donor blood was cross-matched with the recipient and also with the other donor bloods. Under sterile precautions the plasma was aspirated off into a pooling flask; the pipette was then inserted to the bottom of the bottle and the red cells aspirated into a different bottle, leaving the buffy coat or gel, which is composed of leukocytes, platelets and fibrin. All those cells to be used in the same transfusion were aspirated into the same bottle. The cells obtained from one donor blood in this way were called one donor until of concentrated red cells, and hereafter shall be referred to as a donor unit of CRC. Following preparation, the CRC (concentrated red cells) were either used immediately or returned to the refrigerator until used. The CRC were never kept longer than 2 days after preparation.

The CRC were administered in regular Upjohn recipient sets which were equipped with metal screen filters. We did not find it necessary to dilute the CRC prepared in this manner in order to maintain the flow. We varied our regular transfusion procedure only by elevating the reservoir of blood approximately 3 feet higher than the usual level of 3 feet above the antecubital fossa to obtain a greater head of pressure. There was no difficulty in maintaining adequate flow by this method; 30 minutes was the average time required to administer each donor unit of CRC.

Composition of CRC. Listed below is a fairly typical example of the composition of one donor unit of CRC:

Volume	225 cc.
Hemoglobin*	21 9 gm./100 cc.
Hematocrit†	71 3%

* All hemoglobin determinations were performed by the Sahli method.
† All hematocrits were done in Wintrobe tubes.

We have divided our patients into several groups, according to the type of study that was carried out and the amount of cells given.

Group I: In this group only one unit of CRC was given at a time; blood pressure and temperature recordings were taken before the transfusion, the blood pressure after, and the temperature at 1, 2 and 4 hours after its completion. The patient's hemoglobin, hematocrit, non-protein nitrogen, and icterus index were determined before and 1 day after the transfusion; urinalyses were also done on the same days. On the 3rd and 7th days after the transfusion the patient's hemoglobin and hematocrit were again determined.

Group II: This consisted of adult patients who received more than one donor unit of CRC at a time, the children who received CRC in excess of one-half the amount calculated by allowing 10 cc. per pound of body weight, the amount recommended by Holt and McIntosh[6] as being the maximum allowable without danger of overloading the circulation. The same procedure of study was used for this group as in Group I, except that after the 3rd day following the transfusion the hemoglobin and hematocrit were irregularly followed.

Group III: These are patients who received varying quantities of CRC at varying intervals and who were not followed as completely as the previous groups.

Results. *Group I.* Twenty-five transfusions of one donor unit of CRC each were administered to 19 patients. The average rise in hemoglobin the first day following transfusion was 1.22 gm., the 3rd day, 1.18 gm., and the 7th day, 0.86 gm. The hematocrit rise on the same days were, respectively, 3.8%, 3.4% and 2.4%. In a few indi-

vidual cases the non-protein nitrogen rose slightly, but in the whole group averaged a slight decrease. The icterus index rose in a few cases, but generally the increase was slight and insignificant (Table 1). In all patients the urine showed no significant change.

Group II. Twenty transfusions were given to 14 patients. The average increase in hemoglobin on the 1st and 3rd days following the transfusion were respectively, 2.22 gm. per transfusion or 1.05 gm. per donor unit, and 2.04 gm. per transfusion or 0.93 gm. per donor unit. On the same days the average hematocrit rise was 5.5% per transfusion or 2.6% per donor unit, and 5.1% per transfusion or 2.3% per donor unit. The changes in the non-protein nitrogen and the icterus index were approximately the same as in Group I, except for one case in which the icterus index rose considerably following a transfusion reaction (Table 2).

Group III. Seventy-nine transfusions were given to 17 patients (2 of these patients were also in Group II). Among these the results compared favorably with those of Groups I and II. It was impossible to follow many of the patients accurately, since CRC and whole blood were irregularly and intermittently given; also some of the patients receiving the transfusions showed signs of active blood destruction or blood loss. However, from intermittent blood studies as well as clinical observation, it was our impression that transfusions of CRC were as beneficial as whole blood. In Table 3 are listed a number of patients who were anemic, were not bleeding, and who demonstrated no signs of active blood destruction at the time of receiving the CRC transfusions. In these patients the average rise of hemoglobin per donor unit of CRC given was 1.5 gm./100 cc., an increase slightly higher than those of Groups I and II; this would be expected by the type of anemia of the selected patients listed in this table.

Following are the case records of a few typical patients elected to receive CRC:

CASE 1. A 40 year old white male was admitted 8/26/43 to the Medical College of Virginia Hospital with a chief complaint of vomiting and spittin g blood, of 2 days' duration. The laboratory studies showed the hemoglobin was 13.6 gm.; the R.B.C. were 4,810,000; W.B.C. were 7650. A Roentgen ray of the throat revealed a soft tissue mass in the region of the larynx. A laryngoscopy was performed and a biopsy of the mass showed a Grade I carcinoma of the larynx. On 9/6/43 the patient received the first of a series of Roentgen ray treatments, and that night he began to hemorrhage from his throat. This continued intermittently for 6 days, and during that time he received multiple whole blood transfusions to maintain his hemoglobin level. On 9/12/43 the bleeding ceased. At this time the hemoglobin was 3.7 gm. and transfusions of CRC were started. In 7 days seven donor units of CRC were given and the hemoglobin rose to 14.9 gm. The Roentgen ray treatment was resumed on 9/10/43 and a total of 2500 R units were given. On 9/21/43 the patient was discharged for ambulatory treatment.

This represents a case of post-hemorrhagic anemia treated with CRC. The patient received an equivalent of 7 whole blood transfusions in 4 transfusion procedures, in 7 days as CRC. The CRC transfusions were not used to maintain the blood volume or combat shock; whole blood was used for this. The CRC transfusions were started only after it was assured that the blood volume and plasma proteins were normal.

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TABLE 1.—PATIENTS OF GROUP I

Patient	Hemat. of CRC*	Age of CRC* (days)	Gm. Hgb. % Hemat. of patient at intervals: Before transf.	1 day after	3 days after	7 days after	Hgb. rise after 7 days	NPN: Before	NPN: After	Icterus index: Before	Icterus index: After	Reactions
C M 17 Boeck's sarcoid	71.0	3	11.0 40.0	12.3 44.0	12.2 40.0	11.5 42.0	0.5 2.0	33	49	4	14	Sl. chill, temp rise of 3°
C M 40 Pemphigus	64.0	6	7.7 30.0	8.6 31.5	8.2 30.5	7.8 30.5	0.1 0.5	24	?	5	6	None
C M 61 Chronic nephritis	70.0	4	5.9 27.0	7.2 29.5	7.5 ?	7.3 29.0	1.4 2.0	144	124	7	6	None
C F 17 Gon. arthritis	64.0	4	12.0 41.0	13.5 45.0	14.0 45.0	13.0 46.0	1.0 5.0	24	27	4	8	None
C M 61 Chronic nephritis	71.5	5	6.0 26.0	7.2 31.5	6.2 30.0	..	..	102	86	4	5	None
C M 42 Lung abscess	71.0	4	7.0 32.0	8.4 37.0	9.8 36.0	8.4 34.0	1.4 2.0	26	31	5	7	None
C M 22 Diabetes mellitus	76.5	4	5.5 23.0	6.5 26.0	6.3 25.0	5.2 21.5	−0.3 −1.5	34	34	5	5	None
C F 16 Postoperative anemia	73.0	4	7.8 30.0	10.8 39.5	8.7 35.0	8.4 33.0	0.6 3.0	25	26	4	5	None
C F 34 Postoperative anemia	76.0	5	10.8 41.0	11.6 41.0	11.2 40.5	11.0 40.0	0.2 −1.0	28	29	5	5	None
C F 40 Posthemorrhage anemia	71.0	5	6.4 29.0	7.7 33.5	8.5 39.0	8.4 39.0	2.0 10.0	30	28	8	20	None
C M 52 Rheumatoid arthritis	76.0	6	7.5 32.5	8.5 32.0	8.2 32.0	7.8 32.5	0.3 0	27	27	8	10	None
C F 40 Posthemorrhage anemia	75.0	5	6.3 29.0	7.7 33.5	8.2 39.0	7.8 39.0	1.5 10.0	27	24	8	7	None
C M 52 Rheumatoid arthritis	84.0	6	7.4 32.5	8.0 33.0	8.2 33.0	8.0 31.5	0.6 −1.0	26	31	8	12	None
C M 52 Duodenal ulcer	75.0	5	6.4 32.0	7.0 34.0	8.3 35.0	8.2 36.0	1.8	52	50	12	15	None

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C F 40 Duodenal ulcer	75.0	5	9.3 37.5	7.7 33.0	8.2 35.0	7.8 33.0	1.5 −4.0	27	24	3	7	None
C M 52 Rheumatoid arthritis	84.0	6	7.4 32.5	8.0 33.0	8.2 33.0	8.0 31.5	0.6 −1.0	26	31	8	12	None
C M 52 Duodenal ulcer	75.0	5	6.4 32.0	7.0 34.0	8.3 35.0	8.2 36.0	1.8	52	50	12	15	None
C F 47 Cancer of rectum	71.0	3	9.5 35.0	10.4 38.0	10.8 39.5	10.0 39.5	0.5	28	33	5	8	None
C M 33 Paresis	72.0	3	10.9 43.5	12.7 47.5	12.5 47.0	12.3 46.0	1.4	30	32	5	7	None
W M 60 Lymphatic leukemia	73.5	4	12.5 44.5	13.9 47.0	13.0 45.5	..	..	38	42	15	15	None
C F 17 Gc. arthritis	77.5	3	5.3 20.5	6.9 27.5	6.5 25.0	6.1 24.0	0.8 3.5	42	29	6	9	None
C F 18 Sickle cell anemia	69.0	4	5.4 20.0	7.0 28.5	7.3 27.0	7.4 28.5	2.0 8.5	27	25	45	50	None
C M 52 Rheumatoid arthritis	65.0	2	7.8 31.0	8.5 35.0	8.3 33.5	8.1 34.0	0.3 3.0	29	27	10	10	None
C M 49 Luetic heart disease	76.0	2	6.8 26.0	7.8 30.0	7.3 28.5	7.6 26.5	0.8 0.5	78	71	8	8	None
C F 18 Sickle cell anemia	70.0	2	7.4 28.5	8.5 32.0	8.5 31.5	8.0 29.5	0.6 1.0	31	29	50	50	None
C M 44 Pleurisy with effusion	85.0	..	7.3 34.0	9.0 38.0	8.7 38.0	..	..	..	..	4	4	None
W M 31 Typhoid fever	57.0	4	10.0 37.0	11.3 40.0	11.0 ..	10.5 34.5	0.5 −2.5	28	27	20	20	None
W M 45 Melanosarcoma	71.0	4	10.2 34.0	11.1 41.5	11.6 41.5	11.2 38.0	1.0 4.0	34	37	7	8	None

* CRC = Concentrated red corpuscles.

TABLE 2.—CHART PRESENTING PATIENTS OF GROUP II

Patient	Hgb. Hemat. of donor CRC*	Amount given (cc.)	Gm. Hgb. % Hemat. of patient at intervals: Before transf.	1 day after	3 days after	5 days after	10 days after	NPN: Before	NPN: After	Icterus index: Before	Icterus index: After	Reactions and remarks
W M 52 Lymphatic leukemia	21.8 71.0	540	6.5 21.5	8.5 26.0	8.2 25.0	..	..	42	42	25	25	None
" "	23.0 72.0	600	8.2 25.0	8.7 26.0	8.1 24.5	..	..	44	48	15	?	No clinical jaundice
" "	21.5 69.0	600	8.1 24.5	9.8 25.0	..	..	..	44	..	25	25	None
C F 42 "Chronic anemia"	23.0 74.0	700	3.5 18.0	6.2 26.0	4.3 19.5	..	6.7 28.0	26	30	15	15	Clin. icteric 2 days after, soon cleared
C M 4 Nutritional anemia	20.2 70.0	200	10.4 43.0	12.5 48.0	12.0 48.0	11.0 44.0	..	36	40	15	15	None
W F 12 Rocky Mt. spotted fever	21.0 70.0	200	11.1 36.0	11.0 34.0	..	..	..	28	..	10	15	Chill, temp. rise of 2.8°
W M 9 mos. Celiac disease	18.5 68.0	125	8.5 37.0	10.7 43.0	10.8 43.0	..	..	..	..	8	10	None
" "	18.5 68.0	110	10.8 43.0	13.0 46.0	13.5 45.0	..	..	..	..	8	12	None
W F 21 Rocky Mt. spotted fever	24.2 74.0	500	10.4 34.0	12.0 42.0	13.6 44.0	..	..	26	35	8	12	None
C M 5 Sickle cell anemia	18.6 70.5	250	5.2 28.5	8.6 33.5	..	..	..	..	37	50	50	None
W F 21 Rocky Mt. spotted fever	22.6 72.0	500	13.6 44.0	15.0 48.5	14.7 48.5	..	..	35	42	15	20	None
		250	7.5	11.5	11.0			27	28	20	6	None

C M 5 Sickle cell anemia	18.5 30.5 70.5	250	5.2 5.4 28.5	8.6 11.5 33.5	..	..	..	..	37	50	50	None
W F 21 Rocky Mt. spotted fever	22.6 72.0	500	13.6 44.0	15.0 48.5	14.7 48.5	..	..	35	42	15	20	None
C F 3 Sickle cell anemia	.. 64.0	250	7.5 29.0	11.5 42.0	11.0 39.0	..	..	27	28	20	6	None
W F 20 Leukemia	22.0 72.0	450	5.8 23.0	8.1 27.0	..	..	..	37	36	10	12	None
C F 55 Hyperthyroidism	23.5 73.0	450	8.4 30.0	10.5 31.5	..	10.2 35.0	..	34	34	5	8	None
C M 56 Lung abscess	22.5 70.0	600	9.2 33.0	12.5 41.0	12.6 41.0	..	..	33	39	5	8	None
C F 23 Lupus erythematosus	22.9 71.0	525	6.6 28.5	10.1 32.0	..	4.3 18.5	..	48	54	8	10	Very ill before transfusion
C F 49 Postoperative anemia	24.0 76.0	500	8.0 29.5	9.3 29.5	..	..	..	36	?	7	10	None
C M 14 Postoperative anemia	21.2 69.0	450	11.2 28.0	13.1 40.0	..	..	..	30	28	5	5	None
C F 23 Lupus erythematosus	22.8 73.0	450	4.3 18.5	6.5 25.5	..	..	..	54	50	8	7	Very ill before transfusion

Av. rise Hgb. 1st day { 2.22 per transfusion / 1.05 per donor unit }

Av. rise Hgb. 3rd day { 2.04 per transfusion / 0.93 per donor unit }

Av. rise hemat. 1st day { 5.5 per transfusion / 2.6 per donor unit }

Av. rise hemat. 3rd day { 5.1 per transfusion / 2.3 per donor unit }

* CRC = Concentrated red corpuscles.

TABLE 3.—PATIENTS OF GROUP III, SELECTED FROM THOSE WHO SHOWED NEITHER ACTIVE BLOOD LOSS NOR BLOOD DESTRUCTION

Diagnosis	No. of CRC units given*	Total rise of Hgb. in gm.	Av. rise of Hgb. per CRC unit
Carcinoma of larynx—acute blood loss	7	11.2	1.6
Chronic blood loss	6	9.9	1.6
Chronic nephritis	1	1.2	1.2
Leukemia	4	4.8	1.2
Gas gangrene	3	5.1	1.7
Carcinoma of rectum	6	5.2	0.9
Splenic anemia	2½	2.7	1.1
Subphrenic abscess	1	2.4	2.4
Acute blood loss	3	4.0	1.3
Anemia ? ?	2	4.8	2.4
Average rise of Hgb. per unit CRC			1.5

* In several cases 2 units of CRC were given in 1 transfusion.

CASE 2. This 12 year old colored child was admitted 8/4/43 with sickle cell anemia. He had multiple ulcers of both legs, frequent bouts of abdominal cramps, and occasional joint pains. He had been admitted to the hospital in November of 1942 and after receiving multiple whole blood transfusions was discharged very much improved. His blood gradually declined until the present admission, at which time the R.B.C. were 1,870,000 and the hemoglobin was 6.8 gm. The patient was given 3 donor units of CRC and the hemoglobin rose to 10.2 gm.; however, following this, sickle cell crisis supervened as evidenced by acute joint and abdominal pain and severe jaundice. This continued for 3 weeks, during which period the hemoglobin was maintained at about 8 gm. by the administration of 4 donor units of CRC. When the symptoms abated the hemoglobin was 8.2 gm. Three more donor units of CRC were given and the hemoglobin rose to 11.6 gm. On 9/29/43 the patient was discharged with the leg ulcers healed and very much improved symptomatically.

The above is a good illustration of the use of CRC in the maintenance of the hemoglobin during a bout of acute blood destruction. In this case there was no need for replacement of blood volume or of proteins, the only element of the blood required being the red cells. By using CRC in this case (a total of 10 donor units) approximately 2½ liters of plasma that would have been given with the whole blood were saved for more essential use.

CASE 3. This 65 year old white female was first admitted to the Medical College Hospital on 2/2/42 with the complaint of weakness, anorexia, lassitude, and weight loss which had become progressively worse for the previous 8 months. Laboratory studies: R.B.C. 1,200,000, hemoglobin 3.7 gm., W.B.C. 4500. Complete hospital studies lead to no diagnosis other than anemia of unknown etiology. The patient received a series of transfusions and was discharged very much improved symptomatically; however, she was admitted on 5 other occasions during the year, each time receiving multiple transfusions with relief of symptoms. She died 2 days after the final admission on 1/17/43 with pneumococcic meningitis. Her hemoglobin level was maintained for approximately a year with 18 whole blood transfusions and 17 CRC transfusions of one donor unit each. Of the 18 whole blood transfusions, 15 were followed by febrile reactions of a moderate to severe nature. Every available method to discover the incompatibility of the patient's blood was used without success. Of the 17 CRC transfusions only 3 were followed by reactions, and these were relatively mild in nature. Whenever AB blood was available it was used as whole blood; however, frequently this was not possible and Group O CRC were used at these times.

This woman represents a case of anemia of obscure etiology treated by multiple transfusions. It illustrates well the low reaction rate of CRC and the desirability of their use in the rare patient who reacts to whole blood transfusions consistently, with no evidence of incompatibility discoverable; it also illustrates the relatively small danger of using O cells when the blood of a patient's specific group is not available.

CASE 4. A 28 year old housewife was admitted 9/4/43 with a chief complaint of vaginal bleeding and swelling of the face and extremities. There was a severe hypochromic anemia with a hemoglobin of 4.2 gm. On 9/7/43 a dilatation and curettage was done and the bleeding ceased within a few days. The patient received several whole blood transfusions with a moderate rise of hemoglobin level. On 9/10/43 the patient first developed signs of uremia and complete studies revealed renal insufficiency with hydronephrosis and ptosis of the right kidney. The patient then developed congestive failure, and on 9/12/43 her non-protein nitrogen was 124 and the hemoglobin level was 5.4 gm. Because of the congestive failure it was decided that she should receive CRC; in 3 days she received 3 donor units of CRC and her hemoglobin rose to 9.4 gm. With further supportive treatment the uremia subsided, and later other procedures were carried out to correct the ptosis and hydronephrosis of the right kidney.

This represents a case in which there was a need for hemoglobin; however, because of the uremia and congestive failure, there was a danger of overloading the circulation and producing pulmonary edema by large amounts of parental fluids. Transfusions of CRC were advantageous here, furnishing the same amount of hemoglobin present in whole blood in half the volume of fluid. Following the administration of 3 donor units of CRC the hemoglobin rose from 5.4 to 9.4 gm., and with other supportive treatment the uremia subsided.

Reactions. Of the series of 124 transfusions there were 11 reactions, or a total of 8.9%. Nine reactions consisted of chills and fever, 1 was allergic in nature (urticaria), and 1 was a hemolytic reaction 2 days following a transfusion. Of these 11 transfusion reactions, 5 occurred in 20 transfusions given to 2 patients who received CRC primarily because they reacted to the majority of whole blood transfusions, despite all attempts to find a source of incompatibility (Case 3 was one of these patients). Discounting these 2 patients, there were 6 reactions among 104 transfusions, or a total reaction rate of 5.8%. In the first 3000 whole blood transfusions given through our blood bank, the total reaction rate was 7.8%.[7] From these data it may be concluded that the reaction rate with the use of CRC in the average patient requiring blood is lower than with whole blood. We have also observed that the reactions which do occur are usually milder than those which occur with the use of whole blood. An opportunity presented itself to observe this difference in the 2 patients mentioned above; the chills were not as severe or as prolonged and the temperature elevation was less marked.

Discussion. In our series of 124 CRC transfusions we have found that CRC are as efficacious as whole blood in raising the hemoglobin of anemic patients; and in certain instances they possessed an advantage over the use of whole blood. With the use of CRC more

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hemoglobin can be supplied an individual in the same volume of transfused fluids; this reduces the number of procedures and the time necessary to raise the hemoglobin to a given level. However, it was our impression that the hemoglobin rise per donor unit of CRC used was greater when single donor unit transfusions were given over a period of time rather than multiple donor unit transfusions in one procedure. Conversely, the same amount of hemoglobin can be supplied in a smaller volume of transfused fluid. It follows then that CRC could be of definite value in relieving the anemia of patients with a reduced cardiac reserve, by reducing the chances of the production of cardiac failure and pulmonary edema. Theoretically it would also be of value to use CRC in patients who have recently hemorrhaged and in whom there is danger of dislodging a newly formed clot by increasing too greatly the volume of circulating fluid with quantities of whole blood (*e. g.*, bleeding peptic ulcer).

In practically every previous report there has been described a reduced number of reactions with the use of CRC transfusions. This is presumably because the greater portion of the plasma has been removed. We too have found this to be true and have used CRC to advantage in patients who experience reactions to most transfusions of whole blood. It is also well to remember that Group O CRC may be given to patients of a different blood group with less danger of a reaction than with the use of universal whole blood.

Many patients receive whole blood transfusions when only the cellular elements of the blood are needed. If CRC were used for the many cases in which they are indicated, an additional quantity of plasma would be available for other important uses. It has been estimated in the Medical College of Virginia Hospital that about one-half of the transfusions given are to raise the hemoglobin level only. Last year about 3000 transfusions were given; thus, approximately 1500 could have been converted to plasma and red cell concentrates, thereby saving 185 liters of plasma.

It must be realized that CRC transfusions have their limitations. They should not be used in cases of acute blood loss until the blood volume has returned to normal, and the only deficit is in hemoglobin. Their use is contraindicated in shock, burns, and when the plasma proteins are below normal. The uses of CRC are not limited merely to elevating the hemoglobin level; Evans[5] has reported that CRC were apparently as efficacious as whole blood in controlling the bleeding and other purpuric manifestations of the blood dyscrasias. We have observed the same beneficial results in a 12 year old female diagnosed as having monocytic leukemia.

Summary. 1. A procedure for the preparation of CRC is described.

2. It is shown that CRC transfusions are as efficacious as whole blood in raising the hemoglobin of anemic patients in whom only the cellular elements of the blood are deficient.

3. The reaction rate with the use of CRC in the average patient is 5.8% and is 8.9% in the entire series of transfusions to all patients.

4. Certain advantages of the use of CRC transfusions over whole blood are presented and 4 case histories are reviewed as illustrations.

5. The indications for and the contraindications to CRC transfusions are discussed.

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PROGRESS
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MEDICINE

UNDER THE CHARGE OF
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THE SYSTOLIC MURMUR

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The introduction of auscultation of the heart led quickly to the recognition of sounds other than the usual heart tones and an association of those sounds with cardiac damage. It was in 1809 that Allen Burns, a lecturer on Botany in Glasgow, described unusual sounds produced by the heart in a case where the mitral valve was indurated and the pericardium inflamed.[25] He described a hissing noise. Since that time the pendulum of opinion on the interpretation of murmurs has swung from one side to the other. Interest in the significance of these murmurs has been greatest in times of war when the question of physical fitness has reached the importance it routinely deserves.[33]

Levine points out that, when it is realized that patients have compensated organic valvular disease for many more years than they have heart failure and that they often desire to know whether heart disease of any sort exists, the importance of this subject is appreciated.[24b] The great interest in recent years in the efficiency of heart muscle as an index of the extent of damage in the heart has had some effect in minimizing the importance of murmurs. It is sometimes stated that the efficiency of the heart muscle often has greater significance than murmurs in the diagnosis of cardiac disease.[38] This is at times true; but there are also numerous occasions on which the murmur carries greater weight in the diagnosis than does the condition of heart muscle.

Whereas the diastolic murmur has received the greatest respect in cardiac diagnosis, the systolic murmur is known to occur frequently without an anatomic cause. Laennec knew that the murmur was often heard in the absence of heart disease, and we, a century and a quarter later, still frequently find ourselves unable to determine when such a murmur indicates, and when it does not indicate cardiac valvular damage. The early interpretation of cardiac murmurs did not take into consideration transmission of the murmur, history of rheumatic fever, or enlargement of the heart. The differential diagnosis of physiologic and pathologic murmurs was not well established and cardiac murmurs were synonymous with valvular defects. For many years, even though it was recognized that some mur-

murs occurred in the absence of valvular defects, as shown by postmortem examination, the fact that murmurs were sometimes associated with heart disease led to a frequent assumption that a heart with murmurs was a diseased heart. In the period about 40 to 50 years ago the pendulum swung to the other extreme and the teaching became worldwide that systolic murmurs had no significance. It is obvious at present that neither of these extreme views is the correct one and that the truth lies somewhere in between. Confusion in the interpretation of systolic murmurs at the time of the first World War is evident from the fact that at first men with such murmurs were turned down for military service. Through the advice of Lewis, the regulations were later changed so that those with systolic murmurs, in the absence of other evidences of heart disease or a history of rheumatic fever, were accepted.

Frequency. The importance of the problem is reflected in Reid and Pharr's statement that systolic murmurs were found in 20 to 35% of normal youthful patients.[37] Blumenthal[7] found approximately 23% of the patients attending cardiac clinics were normal, and that 25% of these normal individuals had systolic murmurs. Others have estimated the occurrence of systolic murmurs in children at 40 to 70%, and in older age groups at from 20 to 35%.[13]

Rauh[35] found in 710 children from the first to the eighth grade in a school survey in Cincinnati, that 20% had such murmurs. In 5541 high-school students from 12 to 19 years of age, Schwartzman[39] found 134 (2.42%) with organic heart disease, and 43.9% with physiologic murmurs. The latter is a seemingly high figure, which was greatly increased by exercise to 83.6% of those without a murmur at rest. Some believe that especially in children[29] a large percentage of soft murmurs is significant.

Contratto[10] in 2856 college students found systolic murmurs in 350 (12.3%), 7.3% of which were classified as "functional." In 127 (4.6%) the intensity and location precluded a functional classification and there were not sufficient findings to diagnose heart disease. These figures show the importance of the detection, interpretation and evaluation of murmurs as signs of heart disease.

Classification. It has been traditional to term murmurs *organic* when caused by valvular damage, abnormal orifices and constrictions produced by pathologic disturbances in the vascular system. The terms *functional*, *accidental*, *hemic*, *accessory*, *adventitious*, *atonic*, *non-pathologic* and *non-organic* have been applied to the others. Some have classified murmurs by a dichotomous system,[11] first, those occurring in normal individuals, and, second, those found in individuals with disease. In normal persons, murmurs have been further classified into temporary and permanent. In patients with disease, they have been separated into those caused by cardiac disturbances, such as endocardial, valvular, myocardial and congenital disease, and those resulting from generalized disease, such as anemia, hypertension, infection and fever. This system can be simplified by classification of murmurs into 4 groups—those occurring in the absence of disease, those occurring in generalized disease, those resulting from endocardial and from myocardial damage.

White, Adams and Craib[47] have found the terminology in general use unsatisfactory and confusing, a point of view with which the writer heartily agrees. The use of the term *functional*, for example, describes murmurs found in 2 entirely different types of patients—normal individuals and those with a dilated valvular ring or heart chamber from cardiac or extracardiac disease. Such a term, therefore, covers murmurs of no

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importance and murmurs resulting from serious myocardial damage. They propose the following classification:

I. Physiologic murmurs.
  A. Intracardiac or intravascular.
  B. Extracardiac.
    (*a*) Cardiopulmonary.
    (*b*) Pericardial.

II. Pathologic murmurs.
  A. Due to structural valvular disease.
  B. Due to congenital cardiovascular defects.
  C. Due to dilatation of ventricles, aorta, or pulmonary artery from: (*a*) cardiovascular disease; (*b*) other diseases, such as anemia, thyrotoxicosis, severe infection.
  D. Due to pericarditis.

According to this terminology, as further described by White, Adams and Craib, physiologic murmurs are frequently found in normal persons. The intracardiac and intravascular varieties are almost always systolic and occur chiefly over the pulmonic and apical areas. Such murmurs are usually soft and blowing, high pitched, short, often beginning late in the cardiac cycle and ending before the second sound, and are rarely holosystolic. They are heard over a limited area, but at times may be transmitted. Frequently they are inconstant, appear after exercise and vary with the position of the body. They are usually loudest when the patient is lying down and at the end of, or during, inspiration, although they may be heard at the end of expiration. Approximately 50% are heard in both inspiration and expiration. Deep breathing may exaggerate them. They do not replace the first sound.

The cardiopulmonary murmurs of the extracardiac variety result from the action of the heart upon aëration in the lung. They are usually systolic, blowing and relatively faint, but may be transmitted into the axilla. They are at times difficult to differentiate from intravascular murmurs, but if the patient stops breathing at inspiration or full expiration, or even at any point in the respiratory cycle, they usually cease. Sometimes, however, they may continue. Extracardiac murmurs over the heart may be intravascular. Examples of this are the venous hums in the neck which are sometimes heard in the upper chest, and the venous hum transmitted from the epigastrium, occurring at times in the Cruveilhier-Baumgarten syndrome. Occasionally unusual situations occur, such as that described by Maliner,[28] in which a cavernous hemangioma in the left epigastrium produced the murmur. Pericardial sounds are scratching, systolic, diastolic or both, heard just along the left border of the sternum, especially after exercise or in thyrotoxicosis. Explanations for their presence include compression of the pericardial surfaces by the vigorously acting heart.[47]

Pathologic murmurs, as described in the classification of White, Adams and Craib, include some murmurs commonly called functional because they occur with normal valves in cardiac dilatation. It may be difficult or impossible to determine whether or not pathologic murmurs result from deformed valves. Those due to pericarditis are the well-known friction rubs, not usually considered under the term, *murmur*. They are systolic, or systolic and diastolic, in time, scratchy in character, best heard near the left border of the sternum or between the sternum and apex. They will not be discussed here.

The above terminology will be adhered to in the remainder of this

discussion, which is concerned primarily with the problem of differentiation of the physiologic murmur from pathologic murmurs representing cardiovascular disease. This phase of the problem is most important for it is a greater error to make the diagnosis of organic heart disease in a person with a normal heart than it is to make a diagnosis of a normal heart in an individual with a minimal lesion, without any other cardiac findings.[10]

No discussion will be given concerning the factors underlying the development of murmurs. It is well known that when the circulation speeds up to a point where turbulence in flow occurs, murmurs are likely to develop. Since the greatest velocity occurs in systole, the greatest number of murmurs is likely to develop in that time. This point is often reached in exercise, febrile states, hyperthyroidism and conditions causing reduced blood viscosity, such as anemia. Turbulence of flow also results from valvular damage, such as insufficiency or stenosis with constriction of arteries, and from abnormal openings, as in congenital heart disease.

Characteristics of Systolic Murmurs. *Thrills.* Attempts to differentiate physiologic murmurs from the pathologic variety have brought to light many characteristics—some time-honored—which are useful in such differentiation. Most of these characteristics are periodically subject to review[9,22,25] and will be but mentioned here. The presence of a thrill, the palpable counterpart of the murmur, usually brands the murmur as significant. A thrill is not something apart from the murmur, but indicates merely that of the vibrations produced by the turbulent flow, there are enough of sufficient intensity and proper wave length to produce palpable sensations. Intensity, therefore, enters into this concept. All murmurs with accompanying thrills (all thrills, therefore) do not signify organic heart disease. Such vibrations are felt at times in hyperactive hearts, as in hyperthyroidism, or with certain systolic murmurs, especially in the pulmonic area, in the absence of organic heart disease. However, the prolonged purring sensation which is definitely the counterpart of a murmur almost invariably brands that murmur as pathologic.

Quality. Quality and high or low pitch of murmurs, blowing quality, harshness, whistling and musical character[8] are factors of importance in the interpretation of systolic murmurs. It has been suggested that sound records might be helpful in the differentiation of physiologic and pathologic murmurs. McKee[32] points out that the apical systolic murmurs present in cases of mild cardiac damage appear similar to those found in normal records except for increased intensity. She points out, too, that with more advanced heart disease these murmurs become slightly higher in pitch. Manheimer[30] felt that, with filtration of frequency ranges, differentiation could be made between organic and physiologic murmurs and that the method should complement auscultation. Bartlett and Carter[4] profess to differentiate by stethograms systolic murmurs which are significant from those which are not. Criteria are given for this differentiation, but proof of the state of the patient's heart by autopsy is the only safe criterion to check such records and this apparently was not done. Certainly others,[20,48] including the writer, are not convinced of the superiority of sound tracings over the human ear, especially for pitch and loudness, although systolic murmurs may be seen in records when not heard.[19]

At times sound tracings may be helpful by the addition of supportive evidence for a systolic murmur. The diastolic rumble is at times difficult to hear and may be recorded when not audible or when the murmur is

little more than a prolongation of the third heart sound. Likewise events in diastole, split sounds and gallops, may be recognized as heart tones and differentiated from murmurs by the sound tracings.[21,45]

Transmission. Transmission of the murmur adds weight to its interpretation as pathologic. Apical murmurs transmitted into the left axilla and back fall into this group. In some instances transmission is extreme and the murmur may be heard completely around the chest. This phenomenon is described as Couto's circular murmur.[3,34] Further remarks on transmission are included under *Intensity.*

Duration. Two other characteristics of systolic murmurs are of great value in their interpretation. Duration of the murmur is one. A murmur, especially an apical murmur, which persists throughout systole, holosystolic therefore, is usually pathologic. This is particularly true if it replaces the first heart tone.

Confirmatory Reliable Signs of Heart Disease. Finally, and of greatest importance is the presence of other findings diagnostic of heart disease. Cardiac enlargement, a diastolic murmur, alternating pulse, for example, would indicate definite organic heart disease and the accompanying systolic murmur would be considered pathologic.

Intensity. It will be noted that the first 3 characteristics described above were definitely related to intensity of the murmur. The louder the murmur the more likely the transmission. Transmission, especially of apical murmurs to the axilla or back, gives a greater significance to the murmur than if it is localized. Intensity also enters into the obliteration of the first sound when the murmur is instituted with the beginning of systole.

The factor of intensity has received much attention in the interpretation of murmurs. It is not an index of the degree of heart disease, for a slight leakage with vigorous ventricular contraction may give a loud murmur, whereas ventricular dilatation may cause the murmur of great leakage to fade. At times, loud murmurs, even with a thrill, may be heard and yet normal heart valves are found at autopsy.[13] Such circumstances are unusual.

Both Levine[24a] and White[46] give great weight to the intensity of the murmur. Levine feels that all loud murmurs indicate heart disease. He states that we specify the amount and degree of albuminuria and glycosuria in quantitative terms and that the application of the quantitative methods of murmur intensity is also most helpful in diagnosis. He grades murmurs in 6 classes. Grade 1 describes the faintest murmur heard on careful auscultation, which has definite duration into systole to rule out prolongation of the first tone. Grade 6 is the loudest murmur, one which may be heard with the naked ear at some distance from the chest. Grades 2 through 5 are intermediate and are called slight, moderate, loud and very loud. He finds that nearly all murmurs in Grades 3 and 4, or greater, are associated with organic heart disease. In 1000 patients chosen at random from various hospital services, he found that 19.6% had murmurs of Grades 1 and 2. If those with a history of rheumatic fever or with hypertension, anemia, neurocirculatory asthenia, hyperthyroidism and fever were taken out, only 45 (4.5%) remained; and in 34 of these the murmur was Grade 1. He found that in normal individuals, exercise did not produce murmurs above Grades 1 or 2 in 10 subjects tested. Results of this study indicated that if systolic murmurs of Grade 2 or more were found with no conditions such as anemia, hyperthyroidism and the other factors mentioned above, to account for them, they probably were due to some organic change in the heart.

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In 1927, White,[46] upon the basis of intensity, analyzed 1000 patients with apical systolic murmurs, divided into slight, moderate and marked groups. The slight ones constituted 490 of the 1000. Of these, 176 had apparently normal hearts and 276 (56%) had disease. It must be remembered that these patients were chosen from those sent to a cardiologist for evaluation and not at random from the general population. Many of the patients had other evidences of disease such as other murmurs or enlargement of the heart. Moderately loud murmurs constituted 240 of this group. Only 12 were thought to have normal hearts and of the 12, 6 were accounted for on an extracardiac basis. In the very loud group, which included 270 cases, there were only 2 normal hearts, 1 in a patient with anemia. White felt that the louder the murmur, the worse was the prognosis.

Baker, Sprague and White[2] have more recently followed up 187 patients who were seen 10 to 21 years previously with loud or very loud systolic aortic or mitral murmurs, corresponding to Grades 4, 5 and 6 of Levine. Diastolic murmurs were not present. Of these, 155 (82.5%) were dead, and in 122 (78.7%) death had been due to heart disease. In 74 (47.7%) death occurred within 1 year after the first examination; in 110 (70.8%) within 3 years. Only 24 of the 155 deaths occurred under the age of 50. In 24% of the deaths among those with rheumatic heart disease, subacute bacterial endocarditis was the cause. They found that systolic murmurs of this intensity are almost always associated with cardiovascular disease.

Baker, Sprague and White also state that such factors as pregnancy, anemia, hyperthyroidism and neurocirculatory asthenia probably do not produce loud murmurs. Friedlander and Brown[16] carried out several procedures on a number of normal individuals to note the development and intensity of murmurs. In 100 patients with no heart disease, the administration of amyl nitrite to the point of full pharmacologic effect produced murmurs in 47, varying in age from 12 to 57 years. Most of the murmurs were heard at the base and none was louder than Grade 2. In only 4 of 26 patients with fever, produced by typhoid or malaria, did transient systolic murmurs appear, and none was as loud as Grade 3. These data constitute strong evidence in favor of the association of loud murmurs with organic cardiovascular lesions.

The effect of exercise on the appearance of murmurs is not constant. Norris and Landis[16] found that 7.8% of 1552 students developed murmurs after exercise. Mackenzie's figure is 2.8% of 266 apparently healthy students. Siemsen's figure[41a] is 46% in 275 children and adolescents. Schwartzman's high figure[39] of 83% in school children after exercise has already been given.

Location. The location of the systolic murmur is of importance in its interpretation. In the *pulmonic area*, murmurs usually described as functional, that is physiologic, are heard in 60% of children under the age of 14 and are common in thin-chested individuals.[25] These are probably the commonest of all heart murmurs, are usually soft, occasionally rough, frequently loudest with the patient recumbent, and often are absent at some phase of respiration. They are frequently heard best at the end of deep expiration. Usually they are localized and do not replace the first sound. Exercise may bring them out. In this location, such murmurs usually occur without a background of organic disease and are variously ascribed to constriction of the pulmonary artery, dilatation of the artery, or its nearness to the chest wall. At times they may be associated with extracardiac lesions, such as pleural effusion or mediastinal glands,

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which cause displacement or pressure. Pulmonary systolic murmurs due to heart disease may result from right ventricular enlargement, associated with pulmonary disease, mitral stenosis, patent ductus arteriosus or pulmonic stenosis. Because the pulmonic systolic murmur is so frequently found with the normal heart, other evidences, such as cardiac enlargement, diastolic murmurs, thrills or other reliable signs of heart disease, are essential to a cardiac diagnosis. Fortunately, it appears that when the murmur is significant, such corroborative evidence usually is present.

Murmurs in the *aortic area*, unlike those in the pulmonic area, may be difficult to interpret, even when slight transmission into the neck occurs, if other evidences of heart disease are not present. These murmurs are best heard in forced expiration. The writer agrees with Scott's statement[40] that aortic systolic murmurs in adults are so often associated with organic disease that, as a group, it is dangerous to regard them in any other light. Soft systolic murmurs in this area do go unexplained at times, but even then minor changes, rheumatic damage, bicuspid aortic valve, for example, cannot be ruled out. Scott also points out that it is a common error to ascribe systolic murmurs heard in the aortic area to transmission from the pulmonic area. Syphilitic aortitis, aneurysm, arteriosclerotic changes in the aorta, as well as rheumatic aortic disease, may produce systolic aortic murmurs. They may occur at times in the absence of disease, especially in the overactive heart characteristic of such conditions as hyperthyroidism and anemia. In hypertensive patients, also, systolic aortic murmurs may develop. Such a patient may have to bend forward in the sitting position and exhale in order to bring out the murmur. It is evident, therefore, that disease in the region of the aortic valve may, and often does, produce soft, blowing, localized systolic murmurs which, had they occurred in the pulmonic area, would be disregarded. Such a murmur raises the suspicion of disease long before a thrill, musical or harsh quality, transmission to the neck, or changes in the second sound, develop.

The patient's age is of importance in the evaluation of aortic murmurs. In infancy—rheumatic fever and congenital heart disease; in middle age—syphilis and rheumatic fever; and in advanced age—arteriosclerotic changes in the aorta or in the cusps or ring, should be considered. Systolic murmurs of aortic origin may rarely be heard best at the apex; and there are several patients on record in whom aortic disease has produced apical murmurs, at times even with a thrill. Such circumstances are unusual and when aortic murmurs are heard at the apex the intensity is usually greater in the aortic area.[46]

Since the criteria for the establishment of the diagnosis of aortic stenosis by physical means demand a systolic murmur, a thrill and characteristic changes in the pulse, this diagnosis is often not made because of the lack of criteria when the condition is present. With systolic aortic murmurs, this diagnosis is always to be considered and, in the absence of a thrill, changes in the second sound, modifications in the pulse and cardiac enlargement, the systolic murmur may be the only early sign. Under such circumstances, fluoroscopic examination to determine the presence or absence of calcification in the aortic leaflets may be the only means of establishing a diagnosis.

Systolic *tricuspid* murmurs are usually physiologic and intravascular. Organic disease of this valve is rare, whereas systolic murmurs in this region are common. Its ring, for instance, dilates easily with exercise. This occurs so constantly in normal individuals that one would hesitate

to call such dilatation pathologic. The same is true in pregnancy and other states causing increased metabolism. In the cardiac dilatation of disease, a murmur in the tricuspid area is common. Usually the murmur is not conducted widely and has a soft and blowing character.

Systolic *apical* murmurs create the greatest problem in diagnosis because of their frequency and the difficulty in the elimination of the possibility of organic mitral regurgitation.

We have already discussed such characteristics of systolic murmurs as masking of the first sound, transmission, duration and intensity. Constancy of the murmur is known to affect its significance. Definitely pathologic murmurs are often constantly present and little affected by respiration, position and other factors such as tachycardia, which may increase the intensity. Murmurs that are constant from beat to beat and day to day are likely to be harsher, longer and better transmitted. When they are inconstant, they are more likely to be blowing, less intense, localized and heard most often with the patient lying down. The quality and pitch of such murmurs, that is, the presence of harshness and the musical quality,[8] add some weight to the interpretation of the murmur. However, all of these characteristics do not absolutely differentiate physiologic from pathologic murmurs, for it has been established that all the characteristics ascribed to pathologic murmurs may occur at times in the physiologic group. The rare occurrence of loud, transmitted murmurs, with thrills in the absence of heart disease, has already been pointed out.

Certain other characteristics have been described in apical physiologic murmurs, for example, the bridge effect. It has been stated that the localized systolic murmur of nervous tachycardia may at times be heard only when the bell of the scope rests on 2 ribs and bridges the intercostal space.[25] This procedure, when used on a faint systolic murmur, may make it readily audible, when it is otherwise difficult to hear. However, one sees the same effect in more evident systolic murmurs, including the apical systolic murmur of rheumatic heart disease, a fact which indicates that this effect is one of increased intensity of sound, transmitted through the scope to the ear rather than one of differentiation of physiologic and pathologic murmurs.

Certain apical systolic murmurs can readily be determined not to be due to heart disease. This is often, but not always, true of the physiologic, extracardiac, cardiopulmonary murmurs. Since systolic murmurs often occur in conditions which increase the activity of the heart—nervousness, exercise, fever, for example—correlation of the occurrence and disappearance of the murmur with the development and disappearance of the disturbance producing it, indicates the nature of the systolic murmur.

Rheumatic History. From the description of the above characteristics of murmurs which add weight to the interpretation of the murmur as a pathologic one, the deduction may be drawn that the absence of these characteristics usually gives the implication that the murmur is without significance. An inconstant apical murmur which is not transmitted and not related to the factors just above mentioned is commonly regarded as not important. Obviously this is frequently true, as indicated by postmortem examination. But such faint or inconstant, apparently physiologic, murmurs may result from disease. Even when the murmur does not result from heart disease itself, it is important to find the cause, if possible, for the condition causing it, hyperthyroidism, for example, may be as important as heart disease. Faint murmurs classified as Grade 1 are found in many normal people, so that their use in diagnosis is not

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great. Yet they may be associated with organic disease, such as rheumatic fever, and one may not be able to determine from the characteristics of the murmur whether or not rheumatic fever is the causative agent.

Because 20 to 25% of the people with rheumatic heart disease are unaware of a previous attack of rheumatic infection,[40] a murmur produced by rheumatic fever may occur without any historical evidence to point to its importance. With a history of rheumatic fever, one must reserve his opinion[38] and may not, at one examination or over a period of time, be able to determine whether or not an organic lesion is present. Commonly in rheumatic fever several years may elapse after recovery from the acute phases of the disease[13] before definite signs of mitral stenosis appear. At times evidences of rheumatic heart disease may disappear and leave the patient with a systolic murmur only, or no findings. In Bland, Jones and White's series, about 30% of individuals who had rheumatic fever in childhood showed no clinical evidence at a period averaging 10.3 years after the episode.[5,6] In 1000 patients who had had early evidence of rheumatic heart disease in childhood, with such findings as enlargement and mitral diastolic murmurs, 83 (8.3%), at a follow-up after an average of 10 years, showed clinically normal hearts, 30 with faint inconstant pulmonic murmurs, and 53 without any murmurs. A much longer period may elapse with no evidence of disturbance except the systolic apical murmur. Periods as long as 15 years are not uncommon. The usual period is much shorter.

It has been said that one is not usually wrong if he does not diagnose mitral insufficiency, in spite of the presence of a systolic murmur, after a period of several years in which no diastolic murmur has developed and there is no evidence of change of cardiac contour, particularly in the left auricular region, by Roentgen ray examination. In a follow-up study on 100 children with apical systolic murmurs, previously reported by Steuer and Fineberg,[14] they[44] found that 30% developed severe organic disease, but only 9% of those with perfectly normal hearts, fluoroscopically, developed further evidence of heart disease. In 33 followed over 10 years, 27% developed serious valvular diseases, 61% still had systolic murmurs and 12% none. Blumenthal,[7] in a group of patients with systolic murmurs and no associated disease detectable by physical examination, electrocardiography, Roentgen ray examination and laboratory studies, but including those with a history of rheumatic fever, followed up 72 of 100 patients for an average of 7 years. A murmur occurred at the apex in 44 and at the base in the remainder. Only 4 cases, after 7 years' follow-up, developed definite heart abnormalities besides the systolic murmur. He concluded that, if the heart is normal in size and rhythm and there is no sign of organic heart disease, the heart is perfectly normal and that, with other evidences, opinion should be based on other signs and not on the murmur.

However, since systolic murmurs may be present for a number of years without the development of mitral stenosis, a history of rheumatic fever would imply that one could not be assured of the absence of mitral valvular disease in such patients. Even when the murmur is slight and has the characteristics that are commonly ascribed to physiologic murmurs, the patient may carry on a normally long and active life without heart failure or other cardiac impairment. This may be true even when the patient has loud systolic murmurs. The ability to carry full activity and lead a normal, active life does not mean that changes in the valve have not taken place. Under such circumstances, however, it is not necessary to restrict

the patient's activity. The unnecessary production of cardiac neuroses and the wrecking of the happiness of many patients has been brought about by such restrictions. Yet the danger of the development of subacute bacterial endocarditis is evident. Experience indicates that in some of these patients with a systolic murmur, at times having only the characteristics commonly considered physiologic, termination in subacute bacterial endocarditis has shown the real significance of the murmur and the presence over a period of years of minimal rheumatic change in the valves.

Past teaching has emphasized that mitral regurgitation from rheumatic valvulitis is rare without mitral stenosis,[13] particularly after several years have elapsed during which time mitral stenosis is likely to develop. Cabot taught that mitral regurgitation without stenosis was never a justifiable diagnosis. This view would interpret apical systolic murmurs resulting from rheumatic fever as of no consequence, when they frequently are significant.

Since diagnosis on a single sign is never satisfactory and may be impossible, Lendon[23] has stated that, to recognize mitral disease by means of a systolic murmur, it is first essential to eliminate all murmurs which do not arise from the mitral valve and, next, to distinguish between the murmur of a diseased ventricle and that of a diseased valve. For any degree of certainty under such circumstances, a long, harsh, systolic murmur that is transmitted to the axilla must be heard in a patient with a past history of rheumatic fever. Many feel that, if an organic lesion is diagnosed in the mitral valve, stenosis is likely present even though the murmur of mitral stenosis is absent. Diagnoses of rheumatic mitral disease can be, and are, made under certain circumstances in the absence of the diastolic murmur. There is described a widely patent mitral valve with marked regurgitation producing auricular and right ventricular enlargement in the absence of stenosis, as seen postmortem. This is a rare occurrence.

Rheumatic mitral insufficiency cannot be eliminated in a patient with a systolic apical murmur in the presence of a history of rheumatic fever, despite the fact that 2, 5 or even 10 or more years have elapsed, or even when there is no history of rheumatic fever. Such a patient with a systolic murmur may live out his normal expectancy of life, or findings may remain stationary for a number of years and then subacute bacterial endocarditis may develop. Certainly in the absence of a murmur, valvular damage is extremely unlikely. In the presence of a murmur having the characteristics described for physiologic murmurs, the likelihood of organic disease is not great. With the other characteristics described supporting importance of the murmur, particularly with increased intensity and the changes which result with it, the likelihood of the significance of the murmur, even in the absence of enlargement of the heart, is much greater. The arguments for the presence or absence of "pure" mitral regurgitation of a rheumatic origin without some degree of stenosis[12,23] are of little practical importance, for the systolic murmur alone may be evidence of rheumatic heart disease and may be the only auscultatory sign for many years. It is difficult, even after death, to deduce from the appearance of the cusps whether or not leakage occurred in life.

It must be remembered that the diastolic murmur of mitral stenosis is not always easily heard. It may require exercise of the patient or inhalation of amyl nitrite to bring it out and it may be inconstant. If it cannot be heard, fluoroscopic study of the heart may show changes in the left

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auricle and, with the electrocardiogram, help in diagnosis. Calcification of the valves may also be helpful, and in the mitral valve Sosman considers it diagnostic.[42] Such evidences often may point to the importance of a systolic murmur in the absence of any other findings.

Mitral Incompetence. Regurgitation of blood due to incompetence of the mitral valve may result from any lesion which increases the size of the left ventricular cavity and causes either increased tension of the chorda tendineæ, so that the valves cannot close properly, or dilatation of the mitral ring, producing the same effect. In older individuals with arteriosclerosis there may be thickening and sclerotic changes in the mitral cusps which also might produce regurgitation of blood. In arteriosclerotic disease without cardiac enlargement, a systolic murmur frequently occurs.[36] This is particularly true after episodes of coronary thrombosis and some feel that infarction may produce localized dilatation in the mitral ring resulting in the murmur. These findings are likely to develop in older individuals with other evidences to indicate the type of disease, or individuals with obvious types of heart disease, other than rheumatic, with heart failure producing cardiac dilatation. The same finding may occur, as already stated, in anemia with dilatation of the heart. Systolic murmurs almost invariably accompany enlargement of the heart. Thus the factor of age again enters into evaluation of the systolic murmur. Scott[40] feels that the systolic murmur in the patient over 40 should always be suspected as a sign of heart disease. It is evident that one cannot wait for cardiac enlargement to interpret systolic murmurs as resulting from cardiac disease in older individuals. Diagnosis must often rest upon the presence of the cause for the cardiac changes, or upon the basis of the demonstration of calcifications in the valve cusps. The systolic murmur in older individuals, then, may be the only physical evidence of possible damage to the heart by arteriosclerotic disease, and may be the bit of evidence which leads to electrocardiographic and fluoroscopic studies which confirm the presence of myocardial damage.

Systolic Murmurs in Children. The high incidence of systolic murmurs in infants and children has received some consideration in the pediatric literature. Siemsen[41b] points out that the literature concerning physiologic murmurs in older children is fairly extensive but in infants is rather sparse. Explanation of murmurs in infants often entails a discussion of the fetal circulatory structures and of anemia. He quotes Jacobssohn[18] as voicing the opinion that non-organic murmurs are not encountered until after the third year of life. Siemsen examined newborn infants at least twice a week during their hospital stay and found a wide variation in the incidence of murmurs. On one day none was heard in 16 infants and on another 5 of 18 showed murmurs. At times murmurs were inconstant during the examination, as well as from examination to examination. In 26 of 105 (25%) murmurs were heard. The figure increased with the number of examinations per patient; and of those examined once, 12% had murmurs; of those examined twice, 15%; and of those examined 3 times, 37% had murmurs. These murmurs were systolic, mostly soft and blowing and usually loudest over the apex. Occasionally they were loud and at times musical. These findings spoke against the murmurs arising from patent ductus arteriosus or patent foramen ovale where they would likely be basal and of a different quality. No extracardiac causes for murmurs were found. Lyon, Rauh and Stirling,[27] in a similar study, also concluded that patent ductus arteriosus or patent foramen

ovale usually did not produce murmurs at this time. In 7673 newborn infants, they found only 147 (1.9%) as contrasted to the 25% reported by Siemsen, with murmurs in the first week. In older children, physiologic murmurs, as already stated, are common.

Insurance Statistics. Insurance statistics on systolic murmurs show some enlightening data that should be reviewed by all clinicians interested in cardiac examinations. The insurance approach evaluates mortality in a group. McCrudden[31] points out that it may seem odd to the clinician that insurability is based upon murmurs rather than upon a pathologic diagnosis. Where the latter is possible, it does form a basis, but with systolic murmurs the characteristics of the murmur are better established and make a more reliable grouping than do the varied diagnoses inferred from these murmurs by the clinician. In such groups the average mortality is established so that outcome for the group is known and can be predicted, whereas the outlook for any one individual in the group cannot. Clinical medicine deals with the individual, insurance medicine with the group.

Standard risks include those people with no impairment, or with minor ones, accepted at regular premium rates. Substandard risks include impairments of a more serious nature to which some restrictions or extra premium are added. A relative mortality of 150% means 50% above normal, or standard mortality, or an extra mortality of 50%.

Most of the figures quoted on systolic murmurs are based largely upon the medical impairment study (M.I.S.) of a group of companies[1,17,26,31,43] along with some accessory data.[1,15,17,26,43] A decrease in life expectancy has been found with apical systolic murmurs. In persons with an inconstant systolic apical murmur, not transmitted, the mortality was 135%, or an extra mortality of 35%; with a constant murmur, it was 156%. Hence some portion of this group includes murmurs of organic disease. For systolic murmurs in the pulmonic area the figure is only 112%, indicating that murmurs in this area are largely physiologic. When one adds characteristics which clinically are known to increase the importance of the murmur, for example, the constant systolic apical murmur transmitted to the left (but without a history of rheumatic fever), the figure increases to 224%. The mortality is over twice that expected, indicating that such a murmur is a serious impairment. If one adds moderate cardiac hypertrophy, the mortality becomes 476%, or an extra mortality of 376%. Without enlargement, a history of rheumatic fever, or chorea, or other infectious disease runs the extra mortality up to 229%, and with hypertrophy also, to 365%. Mortality is also greater under similar circumstances in heavy workers than in the white collar class. Tonsillectomy seemed to make no difference.

The above figures are, of course, from those presenting themselves for and obtaining insurance, either at standard or substandard rates, and not from the selected type of clientele which would present itself to the cardiologist for check-up. Interpretation of the results is not influenced greatly by arguments that physicians of varied abilities have built up the groups, for the same factor enters into the control series. The figures confirm the clinical discussions of systolic murmurs already given. Pulmonic systolic murmurs without reliable signs of heart disease are so commonly physiologic and so rarely pathologic that one may individualize with the group data and consider such murmurs as generally unimportant in the

individual patient. However, with apical murmurs, even the inconstant ones having characteristics ascribed to physiologic murmurs, the increased mortality indicates that patients with organic heart disease have been included. This fits in with the reluctance, expressed in the clinical discussion of these murmurs above, to accept them as meaningless even though a great or greater portion may be. Such patients are entitled to all the means we have available, electrocardiography and fluoroscopy particularly, to establish a diagnosis, if possible, not with the object of controlling activity or imposing restrictions which may do the patient more harm than good; but with the idea of recognition of the possibility of future bacterial endocarditis, even though remote in time or frequency. Spaced examinations, intelligently advised for the recognition of further progress of findings to a point where satisfactory diagnosis is possible so that early treatment may be instituted if necessary, also result from such a plan. Certainly the statistics also indicate that when the characteristics of murmur transmission and rheumatic history are added, such a plan as just stated becomes imperative. The addition of hypertrophy of the heart places the patient in a category of definite diagnosis and indications for management become immediately apparent.

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NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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PSYCHONEUROSES IN MILITARY PERSONNEL

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THE neuroses which occur in military personnel will be considered in this paper under the following topical headings:

1. Scope of the Problem.
2. Clinical Syndromes.
   - The Traumatic Neuroses.
   - Other Psychoneuroses.
3. Factors Which Tend to Precipitate a Psychoneurosis in Military Personnel.
4. Psychopathology of Neuroses in Military Personnel.
5. Treatment.
   - Prophylaxis.
     - Induction Center.
     - Establishment of Morale.
   - Need for Prompt Therapy.
   - Therapy of the Acute Neuroses.
   - General Measures of Therapy.
   - Special Procedures and Techniques.
   - Group Psychotherapy.
6. Prognosis.
7. Results of Treatment.
8. Rehabilitation of the Neurotic Service Man After Discharge.

1. Scope of the Problem. Psychoneurosis occurring in military personnel was recognized as a major problem in military medicine in World War I[85] and has grown in importance with the progression of the present war.[2,47,50,52] Miller,[87] Kardiner,[62] Gillespie[38] and, more recently, Mira[88] have dealt intensively with the problems attendant with psychoneuroses in wartime. The monograph by Kardiner[62] stresses the chronic traumatic war neuroses and has given us a careful study of these cases from World War I. The book by Miller and his collaborators[87] is based to a large extent on World War I experience, as judged by present-day concepts. Mira[88] has written of his work in the Spanish Republican Army. Further, if available, the restricted monograph by Grinker and Spiegel[46] on War Neuroses in North Africa will be found to contain much valuable clinical and practical material. In general most authors agree that the war neurosis represents a special case of a generalized type of behavior and signifies a failure of adaptation.[113] The primary reagents are the indi-

* Now on active service.

vidual constitution and the environmental set-up of the moment; further, it seems fairly clear that processes resembling conditioning occur in man as well as in experimental animals, and that neurotic states have their own dynamics.[113] The unusual factor regarding war neuroses has not been the type or form of the reaction, since there have been no new clinical entities produced,[15,50] but it is the fact that this war has demonstrated, in the acute war neuroses, that men who have been considered normal may develop neurotic manifestations when placed under excessive fatigue, strain, or emotional upheaval.[50,76,91] However, some writers hold that, without a predisposition, circumstances however bad, do not produce a neurosis.[18,19,47] The tendency toward failure and breakdown has to be regarded quantitatively: in some, it is small and needs considerable stress for its manifestation; in others, it is stronger and becomes manifest on slight stress.[11,15,47,113] The individual constitution determines the form and severity of the neurosis; the momentary environment determines the time of manifestation and to a lesser extent the severity and even the form of the symptoms. Hypochondriasis, depression and anxiety seem to be of all the neurotic symptoms those most directly related to exogenic factors and those which can be most reasonably regarded as a general human weakness, and there are certain circumstances under which it would be abnormal not to be afraid, or depressed, or preoccupied.[113] Military stress has a special tendency to produce anxiety symptoms and some authors[39] feel that the stress can so outweigh the individual personality factors that a heterogenous group of men under the same severe stress can produce remarkably similar symptom pictures.

In the neuroses which develop in military personnel under non-combat conditions, personality factors and predisposition play a large rôle. Careful study of these psychoneuroses reveals that in practically every case the true onset of the disorder took place sometime before enlistment or induction.[96] And although the men who went through severe stress before developing a neurosis do represent a selection for greater constitutional stability, the signs of a neurotic makeup are still to be found (for example, 45% of one such group had a positive family history).[113] In a previous paper[55] appearing in this section, it was possible to cite statistics from several articles on the incidence of positive social history and background data in all neuropsychiatric casualties, combatant and noncombatant, and also in soldiers who broke down only after active duty. The significant factors predisposing to neurotic breakdown are:[30,55]

1. Age. The older age group showed a higher incidence of neuroses.
2. Previous hospitalization for mental illness or previous treatment by a psychiatrist.
3. Previous antisocial behavior.
4. Poor adjustment in school.
5. Poor occupational adjustment.
6. Positive family history ("broken home," mental illness in immediate family, poor economic status).
7. Cerebral concussion.

In almost all papers[1,9,18,19,42,43,44,47,57,75,76,90,113,117] the factor of predisposition is considered. The conclusion reached by all was summarized in a statement of the Surgeon-General: The Army is one of the elements of national defense, and its present mission is one of preparation for an offensive-defensive type of warfare. It is in no sense a social service or a curative agency. It is to be considered neither a haven of rest for

wanderers nor a corrective school for misfits, ne'er-do-wells, feebleminded persons or chronic offenders. Furthermore, it is neither a gymnasium for the training and development of the undernourished or underdeveloped nor a psychiatric clinic for proper adjustment to adult emotional development. Therefore, there is no place within the Army for physical or mental weaklings, potentially psychotic or prepsychotic persons or behavior problems. Men who present behavior problems in the civilian community will certainly present intensified problems in the service.[14]

However, there are as yet no definite criteria for the rejection of men suspected of being predisposed to acute traumatic neuroses.[101] The most careful studies have not revealed a personality structure common to these cases, and it is our belief that the psychologic mechanisms associated with the traumatic neuroses are so fundamental as to be present in all men; hence, as a corollary, the precipitating force lies in the personality's environment and is thus to some extent controllable.[101] The ordinary psychiatric problems of peacetime also occur in the setting of war, and are colored by the war, and here the backgrounds are those of the usual psychoneurosis: childhood insecurity, parental rejection, faulty inheritance, early evidence of maladjustment and immaturity.[101]

2. Clinical Syndromes. *The Traumatic Neuroses.* It must be stated at the outset that many writers do not agree to the separation of the traumatic war neuroses as a distinct clinical entity considered apart from the psychoneuroses which occur in military personnel under non-combat conditions.[6,8,14,15,20,21,22,29,47,75,82,92,94,96,105,110,113,119] However, many of the authors who have returned from actual war experience deal with the traumatic war neuroses as a syndrome in which the psychopathology, the prognosis, and, to some extent, the symptoms differ from that of the non-combat psychoneurosis to such a degree as to place this group under separate consideration.[7,39,56,59,76,91,93,98,114] The article by Raines and Kolb[101] and the discussion by Raines[100] state this point of view well. Further, Kardiner,[62] studying cases of World War I, attempted to separate his cases in a similar fashion.

To delineate this disorder, the combat neurosis, Raines and Kolb[100,101] listed the criteria for the diagnosis of an acute war neurosis: (1) a stable personality prior to the appearance of the traumatically determined emotional disturbance; (2) a combat experience of sufficient intensity to make it a reasonable precipitating agent; (3) objective evidence of subjective anxiety; (4) good recoverability in even a short period of time (3 months) with relatively superficial therapy. The symptoms of a traumatic neurosis can be summarized to include 4 patterns of reaction:[101] (1) The repetitious catastrophic nightmares:[62,68,79,86,101,105,110] these reënact the traumatic scene, are always accompanied by fear which is often childlike in its emotional pattern, and the effect of the fear persists after awakening. (2) The startle reaction:[62,68,79,101,105,110,114] sudden loud noises, day or night, produce a sudden start and also physiologic evidence of anxiety—tremor, dilated pupils, sweat, dry mouth, flush or pallor, palpitation of the heart—and may even give an actual panic reaction. (3) Subtle personality change:[68,79,101,105,110] the patients become morose, silent, sullen, irritable, intolerant of noise or argument, show vacant staring expression, frequently resort to alcohol and frequently are a disciplinary problem; as might be expected, this third symptom is a very variable one. (4) A reaction of guilt accompanied by emotional depression:[79,101,114] this is frequently, but not always, present; it occurs often in survivors of disaster in which a number of the original group were lost, and, in addition to revealing itself

in depression, the sense of guilt also leads to protestations that nothing could have been done for those lost and to the careful exposition of the survivor's efforts to save others.

A further characteristic of the combat neuroses is the rapidity with which new symptoms appear and disappear.[39] It is hard for statistics or classifications to reflect this fluidity of the symptomatology.[113] As time goes on, without treatment, a more stabilized syndrome results. Potter[98] defines a traumatic war neurosis as a massive explosion of anxiety or fear at a primitive psychologic level, producing a psychosomatic disorganization of the entire organism; it is precipitated by a catastrophic threat to the total organism and preceded by psychosomatic tension and fatigue for a period during which the subject is both consciously and unconsciously poised, mentally and physically, for offensive or defensive action. Psychosomatic disorganization is reflected in symptomatology related to disturbances of the conscious or ego mental functioning; the emotional organization; and those somatic structures dominated by the autonomic nervous system. The autonomic and psychologic disturbances, in turn, provoke secondary anxiety, conscious in nature, thus creating a widespread subjective insecurity which further disorganizes the ego. Finally, the conscious anxiety and generalized subjective insecurity, with its concomitant physiologic and psychologic tension, serves to feed the basic psychosomatic disorganization and to perpetuate the primary physiologic and psychologic disturbances.[98] Kardiner[62] states that the traumatic neuroses results from contraction of the executive functions of the ego, and that this involves that aspect of ego functioning which deals with the interpretation and mastery of the outer world; the patients approached any activity with a view in which they appeared utterly helpless and their world dangerously hostile. The traumatic neurosis may be superimposed on the neurotic background but the two conditions are different and can be readily distinguished; later on, in the chronic stages, the two neuroses may become fused and difficult to distinguish but they must still be treated individually in keeping with their respective psychopathologic construction.[7]

Other Psychoneuroses (in which the individual's personality and not combat is the major etiologic agent). Military service furnishes an excellent medium for the growth and development of a psychoneurosis in a susceptible personality.[14,57,62] The psychoneurosis is thus a pattern of adjustment which the person makes to the problem of living in a military environment and represents a failure of adaptation within the personality which gives rise, owing to emotional conflict, to symptoms which may be of conscious or unconscious origin.[8,69,91] These neuroses are typical of the neurotic illness seen in civilian life,[93] except that anxiety, panic states and reactive depression seem to be more common in the service than in civilian life.[27,29] There are strong correlations, statistically, between the makeup of the personality and the symptoms exhibited in the neurosis.[1,113] These psychoneuroses fall into the usual types seen in civilian psychiatry, the most common forms being: (1)the anxiety states, (2) the conversion hysterias, and (3) the reactive depressions.[13,20,21,39,50,57,74] In order to group the acute and chronic war neuroses in a single classification, Whitehead[124] used anxiety as the basic factor and arranged the psychoneuroses in 3 groups: (1) neuroses in which anxiety shows itself directly as a symptom (anxiety states, fear states); (2) neuroses that are defenses developed in the individual against the direct manifestation of anxiety (conversion hysteria, compulsions, phobias, hypochondriasis and regressions to earlier childhood patterns of behavior); (3) neuroses which present

the by-products of the struggle between anxiety and the defenses against it (neurasthenia, fatigue states, mild depression).

3. Factors Which Tend to Precipitate a Psychoneurosis in Military Service. Almost every article on the non-combat neuroses stress the rôles played by the individual's own personality background and his constitutional predisposition. However it is universally recognized that military service has inherent factors which tend to precipitate a neurosis. Knight and Orr,[67] Billings[9] and Pignataro[96] have all written excellent articles discussing these factors. In summary, the factors during the training period are:

1. Separation from home ties.
2. Anxiety over home responsibilities and family.
3. Change in habit routines.
4. Necessity of submission to authority and discipline.
5. Loss of prestige and other "narcissistic" blows.
6. Contacts with other men without any privacy.
7. Guilt over feelings of aggression.
8. Exhaustion and monotony.
9. Sex deprivation and sex conflicts.
10. Arousing fears of bodily injury or death.

The precipitating factors in the combat zone are:

1. All of the factors of the training period.
2. Insufficient period of training for combat.
3. Fear of his own cowardice.
4. Disappointments and feelings of frustration.
5. Lack of faith and confidence in leaders.
6. Increased fatigue.
7. Increased responsibility.
8. Poor food and poor sanitation.
9. Exposure to explosions, blast and gases.
10. Effects of climate, and of somatic disease.
11. Repeated narrow escapes following one another in rapid succession.

The articles dealing with these above factors were summarized in this section a year ago,[55] and since then there have been other articles discussing these factors.[35,58,62,65,80,101,105,123,124]

4. Psychopathology of Neuroses in Military Personnel. Just as in civilian neuroses, anxiety is the important causative factor in the neurotic illness.[43,64,96,100,124] However, the emotional conflict producing this anxiety does have certain factors peculiar to the military situation.[34,80] The following are some of the psychopathologic factors which seem to be important in the causation of anxiety in military personnel:

(*a*) *The Conflict Between Acquired Social Attitudes and the "Instinct" of Self-preservation.*[14,41,43,65,105,120] Miller[87] states that frequently the neurotic patient had stuck to his duty until the controlling force was no longer able to stand up against the insistent demands of an instinct which demanded either an escape from danger or an aggressive outburst. He also considers the rôle of self-love and other emotional conflicts. Williams[125] feels that there is first a basic personality structure characterized by self-centeredness, overconscientiousness, lack of sociability and lack of affection for relatives and friends. The unconditional demand for self-sacrifice in war means a renunciation of narcissistic privileges which these individuals cannot do. They have a diminished capacity for external interests and emotional ties, and an increased self-centeredness which is expressed in the neurotic illness. As Thom[120] says, in order to be adequate and to fulfill the purpose of protection for which it is psychologically designed, the neurosis allows the soldier to escape from the intolerable situation

created by impending danger and to accomplish this without loss of self-respect.

(*b*) *The Traumatic Factor.*[31] Often the traumatic experience is one which serves to precipitate a psychopathologic reaction through the activation of preëxisting but hitherto latent psychopathologic factors. In certain cases it is possible to detect a very high degree of specificity in the traumatic experience.

(*c*) *The Factor of Infantile Dependence.*[31] Fairbairn[31] feels that there is a close relationship between the development of a war neurosis and the persistence of infantile dependence. This has also been found present in cases of malingering.[40] The neurotic symptoms are seen as essentially either effects of, or defences against the conflicts attendant upon a persistent attitude of infantile dependence in the emotional sphere. This gives rise to a common basic symptom of separation-anxiety; the soldier becomes ill because he craves to go home. Further, the capacity to endure danger varies with the extent to which the individual has outgrown the stage of infantile dependence. This factor has been recognized also in articles by Flicker and Weiss[34] and by McKerracher.[83] The latter author[83] writes that so active is the protective mechanism of the neurotic that some wag has translated D.A.H. to mean not "disordered action of the heart," but rather, "desperate affection for home." Fairbairn[31] feels that much of the symptomatology of the neurosis is the expression of the compulsiveness of the desire to return home.

(*d*) *The Factor of Identification.*[31] By identification the individual tends to identify himself emotionally with, and *pari passu* fails to differentiate himself from those on whom he depends. The original identification of anyone is with his mother (and later his other parent and parent substitutes). When emotional development is satisfactory, there is a progressive decrease in identification, accompanied by a progressive increase of a capacity on the part of the individual to differentiate himself from emotionally significant figures. Emotional maturity is consequently characterized not only by a capacity to sustain relationships with other individuals on a basis of mutual independence but also by a capacity to contract fresh relationships. These capacities are deficient in the individual who fails to outgrow the stage of infantile dependence. Hence such a person, when placed under military conditions, finds it too difficult to establish himself as a separate personality within the framework of the military organization, subordinate himself to the aims of the military group without any surrender of individuality, and maintain stable emotional bonds with the group while remaining differentiated from it. On the other hand, he also usually finds great difficulty in either establishing or maintaining a reliable relationship with the military group on the basis of identification. This is due, of course, to the fact that his identification with his home and his loved ones proves too strong to admit of a competitor; and it is to the strength of this identification to his home and loved ones that above all the development of a war neurosis must be attributed.[31]

(*e*) *The Factor of Morale.*[31] In the case of the "normal" soldier, acute anxiety occurs only when the bonds uniting the group as a whole are dissolved. Each quondam member of the group becomes thus deprived of the support both of his fellow-soldiers and of the military group as a whole, and is relegated to the status of an isolated individual facing the combined strength of a hostile force without any support. Confronted with such a perilous situation, the soldier may be assailed by panic. Thus, even a "normal" soldier may develop a war neurosis, albeit a transient one, in circumstances in which morale becomes impaired. Further,

the existence of a high state of morale within a group can exercise a profound influence in counteracting the ill-effects of infantile dependence among its members. However, in the case of a neurotic soldier, separation-anxiety may occur even when the bonds uniting the group as a whole remain intact. This means, of course, that the bonds uniting the neurotic soldier to the military group are unduly slender and precarious, because he has retained from childhood an excessive degree of infantile dependence.[31]

(*f*) *The Super-ego Factors.*[31] Once the neurosis is established there is a remarkable absence of guilt over the evasion of military duty involved. The only exceptions to this are in cases with depressive and obsessional features; and in the prodromal stage of the war neurosis, where there is still real conflict between the desire to return home and the sense of duty. What happens is that the neurotic soldier regresses, in a greater or lesser degree, to a level of infantile development at which the structure of conscience has not yet been organized on a stable basis. The neurotic soldier is thus more or less reduced to the emotional state of a child who has not yet reached the stage of accepting his parents as authoritative conscience-figures and hence he does not regard the military organization as an authoritative parental figure to whom he is bound by a deep sense of moral obligation. Rather, he begins to regard his officers as "bad" parental figures who have no love or consideration for him. At the same time he identifies those at home as "good" parental figures who love him and who will look after him if he can only get back to them. Thus he becomes consumed by an overwhelming desire to escape from the insecurity which he experiences at the hands of the "bad" figures—into whose clutches he feels that military obligations have delivered him—to the security which the "good" figures at home seem, by contrast, to offer him.[31]

Treatment. In order to treat any patient successfully, whether in civilian or military life, the physician must first understand his own emotional attitudes and conflicts; in order to help the physician clarify his feelings upon entering military life, Menninger[84] has discussed some of the problems in adjustment which he will meet. Further, there are many articles which survey the general administrative duties of military psychiatry,[24,45,49,54,97] and others which stress the prophylactic value of a competent neuropsychiatric examination at the Armed Forces Induction Center.[54,55,74,75,77,126] The factors leading to the establishment of good morale have been considered and the following have been found to be important.[23,33,67,73,74,75,79,80,81,89,101,118,119,122]

1. Adequate training in order to develop confidence and skill.
2. Prevention of fatigue and monotony.
3. Keeping the men occupied either in constructive play or useful training.
4. Giving the men some degree of psychologic self-understanding regarding the problems of fear, sex and war motives.
5. Classification of men to duties chosen according to the mental and emotional capabilities of the individual soldier.
6. Elimination of men with manifest personality disorders.
7. Establishment of group morale by appreciation of and faith in the ideals and goals for which the war is being fought, by setting up clear and simple common goals of personal significance to each soldier, by stressing positive and not negative drives: love and ideals, not fear and hate.
8. Provision of adequate diet, rest, medical and personal care and recreation.
9. Establishment of identification with the group, and loyalty to it and the officers.
10. Personal interest in the men by the officers.
11. Instruction in psychiatry for general medical and line officers.

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The use of a mental hygiene, or special training, or rehabilitation unit can be of great value when it is properly established and when the staff includes psychiatrists, psychologists, vocational guidance officer, occupation therapist, and psychiatric social workers.[35,36,57,104,118,128] Further, the establishment of an out-patient psychiatric service, an adequate consultation service, and a Barracks psychiatrist are all worthwhile prophylactic measures.[36,128]

When we concern ourselves with the actual treatment of a neurosis in military personnel the first axiom, and an important one, is to treat promptly and as near the site of the inception of the neurosis as is feasible.[5,39,56,67,89,91,102,120] The second rule is to separate the neurotically ill soldier from his healthy comrades as soon as possible in order to maintain group morale.[5,17] The third basis of treatment is that the length of stay in the combat-zone hospital is kept as short as possible (2 to 21 days),[91,120] in order to prevent the fixation of the protective mechanisms and the development of the neurotic personality pattern.[17,39] Likewise the medical officer expresses optimism and coöperation but is not too sympathetic (stern kindness) and he establishes some form of work program as soon as possible.[5,91]

As to the actual therapy which should be carried out promptly on the acute combat neuroses, there are two basic principles: (1) the giving of complete physical and mental rest;[15,17,50,59,66,68,98,101,106,107,108,109,125] (2) the restoration of normal body metabolism and nutrition.[17,50,59,66,68,98,108,109,125] The rest is given in bed, with maintenance of adequate bodily warmth, and with sedation in sufficient amount to secure deep sleep of at least 10 hours' duration and sometimes extending for 48 hours.[109] Sedatives which are used are the intravenous barbiturates, or paraldehyde by mouth or rectum, or sodium amytal by mouth.[66,108,109] This deep sleep is often followed by 1 or 2 days of milder sedation.[108]

The normal body metabolism and nutrition is restored by use of food and fluids in large amounts, the use of intravenous fluids and plasma.[66,109] If necessary, continuous sleep treatment can be used also.[68,109] An important factor is weight loss and progress can be judged by its restoration.[109]

After the patient has recovered from his exhaustion, then the psychotherapeutic measures can begin: these include in the early stages the use of reassurance and support,[66] catharsis,[28,47,66,68,101,107] hypnoanalysis[32,47,66,68,127] and narcoanalysis.[4,32,47,66,68,127]

Catharsis allows for emotional desensitization of the patient to the traumatic experience, and regardless of the improvement gotten by rest, this desensitization should be begun immediately thereafter.[101] It consists simply of encouraging the patient to tell of his combat experience in an atmosphere of mutual understanding and respect.[101] It gives release from obsessive waking nightmares, from obsessive guilt feelings and from rage; it allows a return to the sensations of real life.[68] If hypno-narcoanalysis is used, it is done for a fourfold purpose: (1) to allow the patient to express feelings of which he may be dimly aware yet afraid to express; (2) to allow the patient to become aware of feelings which he may have buried so completely as to be totally unaware of them but which may nonetheless disturb him; (3) to allow the patient to express these deeply buried and unconscious feelings; (4) to penetrate into the amnesic areas of the patient's psychologic processes in order to "waken" that aspect of the personality and those mechanisms of control which were rendered inaccessible by the traumatic experiences.[68] The recovered material must be fully fused with its appropriate emotional content and with normal waking consciousness;[68]

it is indispensable for cure that the dissociated or repressed thoughts be brought into consciousness after the resistances have been broken through.[4,32,47,66]

After the patient has been evacuated from the combat zone, certain other psychotherapeutic measures can be utilized along with the above-mentioned ones. Up to this point in the treatment the primary aim of therapy was to restore the patient to combat duty; now the primary aim becomes one of rehabilitating the patient for civilian life in a productive capacity.[66] Treatment now proceeds with a carefully taken psychiatric history and a complete physical and mental examination, including psychologic testing, so that a proper evaluation of the patient's capabilities can be made.[66,125] If possible, a social history[128] with report of the patient's pre-war personality and adjustment are included.[24,76] The patient is encouraged to give the onset and development of his illness in utmost detail, and this often serves as an opportunity for an out-pouring of pent-up emotions.[2,121] In the treatable cases, active psychotherapy is carried out by attempting to explain the nature of the illness to the patient. An endeavor is made to concentrate the patient's attention on the fact that his state is the result of normal fear in a sensitive individual, and that in his endeavor to control that normal fear by calling up forces by sentiment, self-respect, social tradition, or morale, he has displayed courage rather than cowardice. Care must be taken not to appear too sympathetic and while reassurance and explanation are helpful, the patient must be made to realize that he is expected to recover and that ultimately he himself must climb back to the manhood level from the infantile level to which he has, for the time being, regressed.[2,51,61] Further, occupational therapy,[112] vocational training and educational training are all useful tools.[2,24,66,76,127] Recreational therapy through both individual and group games and sports is of value;[66,127] this recreation should be largely the result of the patient's own efforts (a concert by patients is better than a movie).[24] In those patients who are not accessible to ordinary psychotherapy, shock therapy is used: electric shock therapy,[108,109] modified insulin therapy,[108,109,125] and the usual insulin treatment.[66] Often the shock therapy is discontinued as soon as the patient becomes accessible to direct psychotherapy.[5,107] Sometimes many of the phenomena of the acute war combat neuroses appear to be acute states of partial dissociation, which precipitate the patient into a waking nightmare from which he cannot be aroused; such patients can be made accessible to contact by insulin therapy or electric shock treatment and the methods should be used as soon as the state is recognized and before it becomes chronic.[68] In the excitements, prolonged sleep under continuous narcosis may be helpful,[68,109] although the results have sometimes been disappointing.[17] The sleep must be deep so that it is not disturbed by nightmares or obsessional horror reveries, and it is sustained for several days, maintaining at least 20 hours sleep in each 24-hour period but allowing the patient to be roused for meals, fluids and elimination.[68] Psychoanalysis of a war neurosis is used but it should not be undertaken unless one is prepared and competent to complete the therapy and to unearth the nucleus of the underlying, formerly latent psychoneurosis.[8]

The use of group psychotherapy is becoming more and more prevalent in the treatment of the war neuroses,[59] and seems to be applicable to a large per cent of the cases.[53] Several fairly comprehensive articles have appeared on this method of therapy.[10,12,53,60,115] and the exact technique used varies with each author. There is a general agreement in the litera-

ture that individual psychoanalytic procedures do not fulfill all the therapeutic needs of the patient;[59,68,100,105,111] all those problems and conflicts which come roughly within the domain of the social super-ego do not seem to get properly worked out.[111] One of the main distinctions in treatment implied in group therapy is the introduction of a didactic element.[111] The basic plan for a group therapy program consists of: first, preliminary diagnostic and therapeutic interviews with each individual patient; then a course of several lectures given to the group by the physician during which various methods of participation by the group in the discussion are used; individual interviews given to most of those patients who do not show satisfactory improvement during group treatment.

Prognosis in the Neuroses Occurring in Military Personnel. There are several factors which favorably influence the prognosis in the war neuroses:

1. The sounder the integration of the premilitary personality, the better the prognosis.[119]
2. The more severe and continuous the combat experience before the break occurs, the better the prognosis.[119]
3. The more marked the exhaustion, deprivation, and in general the somatic factors, the better the prognosis.[119]
4. Prognosis is better in the anxiety neuroses and conversion hysterias than in the neurasthenic-hypochondriacal states and the obsessive-compulsive reactions.[119]
5. Prognosis is better when the man has a certain period of time in which to "digest" the emotional turmoil of one traumatic experience before being exposed to another.[101]
6. Prognosis is better when the psychiatrist is able to transfer a man from one unit to another on psychiatric grounds, to arrange his allotment to duties particularly suited to the man, and to recommend him for a station in the neighborhood of his own home.[25,113]

The prognosis in the neuroses of war is unfavorably influenced by the following factors:

1. The longer the time elapsing between the occurrence of the casualty and the initial psychiatric aid, the worse the prognosis.[119]
2. Beyond a certain area, the farther a casualty is removed from the zone of combat, the poorer the prognosis.[101,119]
3. All symptoms are liable to be aggravated in the presence of loved ones, friends, relatives, spouse, or family. In such a situation the traumatic anxiety attaches to the emotional ramifications of family life and may become irreparably fixed.[101]
4. The prognosis is poorer if the "war neurosis" becomes incorporated with any underlying emotional conflict, or mental deficiency, or incipient psychosis, or organic brain damage.[101]
5. The prognosis is poorer in patients with a poor heredity, or with unfavorable personality traits before service, or with constitutional predisposition, or with difficulty in adjustment prior to service, or with strong resentment of military service.[71,91]
6. Recovery is consciously or unconsciously resisted, since this means a return to the rigors of duty.[3]
7. Treatment is free; a patient makes no financial sacrifice; he need concontribute nothing toward his cure; therefore, the treatment has "no value" to him.[3]
8. It is difficult to effect a permanent or personal relation between physician and soldier because of frequent change of station by both. A feeling of permanence or a sense of follow-up responsibility is missing.[3]

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9. A patient goes through the hands of many different physicians and their varying points of view.[3]
10. The soldier feels he is being treated by the same agency responsible for his plight.[3]
11. Negative suggestion by other patients.[3]
12. The presence of secondary gain in the illness through pensions and compensation which continue in effect so long as and only if the neurosis continues.[3,22,66,72,79] If any compensation is given to neurotic patients it should be on a one-lump-sum basis.

Results of Treatment. The statistics on the per cent of the various types of psychoneuroses who return to full duty or are returned to limited service are probably unavoidably unreliable because psychiatrists in the forward area and even in the general base hospitals have almost no opportunity to follow up their cases with sufficient accuracy and over a long enough period of time.[71] Further, it is difficult to judge the therapy on the basis of the per cent returned to duty because it depends greatly on the type case with which the psychiatrist is working. However, in Table 1 we have compiled the results of treatment as given in the literature. In addition, Smith[114] reporting on cases from Guadalcanal said that very few of the patients would be able to return to combat duty and only 10 to 15% would be able to return to limited duty. Sutherland[26] in 1941 reported only 9% of his patients as fit to return to full duty after treatment at a neurosis center. In contradistinction to this, we have had recent reports of 60%, and even 75% of the war neuroses treated in the combat zone returning to duty.[105]

Rehabilitation of the Neurotic Service Man After Discharge From Service. There have been encouraging steps taken toward the handling of this problem within recent months. The formation of a Division of Rehabilitation by the National Committee for Mental Hygiene, and the increasing awareness of the United States Employment Service in this problem, and the formation of rehabilitation clinics in New York and Massachusetts, with plans for other such clinics in Wisconsin, Connecticut, Vermont and Colorado—all of these are extremely favorable signs. However, there exists a need for national planning for psychiatric rehabilitation and this is the service which Rennie is beginning to supply.[103] The Barden-LaFollette Vocational Rehabilitation Amendment was approved by the President on July 6, 1943, and makes the mentally disabled, as well as the physically disabled, eligible for rehabilitation.[103] Rennie[103] feels that there are 5 major needs existing in regard to adequate psychiatric rehabilitation; these are: (1) the scarcity of psychiatric help available; (2) the time-lag between discharge and beginning of treatment; (3) the need of a total psychiatric and physical survey for these men; (4) the need for community coöperation in this endeavor; and (5) the need for a closer liaison relationship with the Army and the rehabilitation agencies.

The rôle of the psychiatric social worker in rehabilitation is a major one and has been recognized.[48,128] There have been a few articles[97,120] in the literature on a rehabilitation program for the discharged soldier; those by Sommer and Weinberg,[116] Rickles,[104] Preston[99] and Pratt[95] are good. That the soldier discharged on account of neurotic illness needs such a rehabilitation program is shown by the English survey which revealed that in 120 soldiers discharged with a diagnosis of psychoneurosis, 50% had made an unsatisfactory social adjustment in civilian life;[70] further, 12% of them were unemployed and 51% of those employed earn less than they did before enlistment.[70]

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TABLE 1.—RESULTS OF TREATMENT OF NEUROSES IN MILITARY PERSONNE

Reference No. and Date	Type of neurosis	Improvement				Disposal			Follow up		
		None (%)	Slight (%)	Great (%)	Recovery (%)	Return to duty (%)	Transferred (%)	Invalided (%)	No. observed	Success (%)	Failure (%)
113 Jan. 1943	Anxiety neurosis	14.6	42.5	33.2	9.7	26.5	1.0	72.5	122	52.5	47.5
	Hysteria	17.7	40.9	20.0	15.4	25.2	3.1	71.7	77	50.7	49.4
	Reactive depression	16.6	39.0	31.6	12.7	22.3	2.8	74.9	40	60.0	40.0
120 World War I	All types of psychoneuroses	..	..	..	..	65.0	30.0	5.0			
7 July 1943	Traumatic neurosis	9.0	42.0	30.0	19.0	57.0	16.0	27.0			
75 Aug. 1942	Hysteria	..	..	..	..	44.4	..	55.6			
	Fear or anxiety states	..	..	..	..	55.8	..	44.2			
5, 24 Aug. 1942	War neurosis treated in combat zone	..	..	..	..	60–65	20–25	10.0			
5 Sept. 1941	War neurosis treated in hosp. in interior	20.0	15.0	65.0							
25 Dec. 1940	All types of psychoneuroses	..	..	..	..	33.0	67.0				
24 Aug. 1942	All types of psychoneuroses	..	..	..	..	61.0	23.0	12.0			
	Hysteria	..	..	..	..	77.0	20.0	3.0			
	Anxiety states	..	..	..	..	55.0	30.0	10.0			
75 Aug. 1942	Hysteria	..	..	..	..	44.4	..	55.6			
	Anxiety states	..	..	..	..	55.8	..	44.2			

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF MAY 16, 1944

Factors Affecting the Determination of Oxygen Capacity, Content, and Pressure in Human Arterial Blood. F. J. W. ROUGHTON, R. C. DARLING, and W. S. ROOT (Fatigue Laboratory, Harvard Univ. and Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ.). The percentage saturation of the arterial blood is usually obtained by dividing the O_2 content, as determined gasometrically, soon after the sample is withdrawn, by the O_2 capacity determined some time (often an hour or more) later. We have no changes to suggest in the Van Slyke determination of O_2 content, but we have found 3 factors all of which cause the oxygen capacity of blood, as determined by the usual method of rotation with air in a tonometer, to be greater than its presumed value *in vivo* before withdrawal from artery or vein:

1. The blood which drains to the bottom of the tonometer, when this is stood up for withdrawal of the sample for analysis, contains a slight excess of hemoglobin, owing to the fact that plasma sticks to the walls of the vessel better than do red cells. This has been proved by direct analysis of the Hb and total N of the dregs.

2. Normal human blood (especially that of smokers) contains traces of COHb, which dissociate to a very slight extent during rotation with air. The effective O_2 capacity hence increases correspondingly. Under average conditions these 2 factors cause a total apparent increase equal to about 0.8% of the total capacity.

3. Reversion to normal hemoglobin of some of the 3% (average figure) inactive fraction of hemoglobin established to be present in normal human blood by Ammundsen (*J. Biol. Chem.*, **138**, 563, 1941) and ourselves. The extent of the reversion varies unpredictably but averages 1 to 1.5% of the total hemoglobin.

The sum of the 3 effects would be expected to be about 2%, which would raise the average figures for the per cent O_2Hb in arterial blood from 95 to 97, at sea level. The pO_2 corresponding to 97% O_2Hb is 98 mm., if read off from a standard dissociation curve; this value is very close to the average figure for the alveolar pO_2 of normal man at sea level. We believe that the previously claimed differences of 20 mm. Hg between alveolar air and arterial blood at sea level are in error, through inattention to these 3 factors. In view of the difficulty of allowing for these factors satisfactorily in given instances, it seems doubtful whether the continued use of the dissociation curve for determining arterial pO_2 at sea level is desirable; this caution does not, however, apply to experiments at altitude, where the per cent O_2Hb is below 85, since in this range an uncertainty of 2% O_2Hb only affects the determination of pO_2 to the extent of 2 to 3 mm. For sea level determinations of arterial pO_2 it would seem that wider use should be made of aërotonometer methods.

Owing to the smallness of the reversion effect we have as yet no data as to the nature of the hemoglobin compound involved (*e. g.*, is it in whole or in part methemoglobin?) nor do we know how it varies in exercise, acclimatization to high altitudes and pathologic conditions.

Spectrophotometric Observation of Circulating Blood in Vivo, and the Direct Spectrophotometric Determination of the Saturation of Hemoglobin in Arterial Dog Blood.* DAVID L. DRABKIN and CARL F. SCHMIDT (Depts. of Physiological Chemistry and Pharmacology, Univ. of Penna.). Uncertainty exists at present concerning the degree of saturation of arterial blood at sea level. The usual gasometric technique for determining the percentage of saturation of hemoglobin with oxygen is indirect. Two separate analyses, *oxygen content* and *oxygen saturation*, are required. (*Oxygen content/oxygen capacity*) × 100 gives *percentage saturation*. Several criticisms of this procedure may be made. Uncertainty in *percentage saturation* of arterial blood leads to uncertainty in the value of its *oxygen tension*, usually read off from previously determined oxygen dissociation curves, which relate saturation to tension. The portion of the dissociation curve which applies to arterial blood at sea level is asymptotic, so that 2 to 3% difference in saturation corresponds to a difference of 20 to 30 mm. in oxygen tension. In seeking additional information upon arterial saturation, we have turned to the spectrophotometric analysis of arterial blood. The optical technique is particularly appropriate for the direct quantitative determination of 2 or more species (in the present work, HbO_2 and Hb) in a solution.

* Work done under contract with the Office of Scientific Research and Development.

The continuous direct spectrophotometric observation of circulating blood *in vivo* has been successfully carried out. For this purpose the Drabkin and Austin special cuvette of 0.007 cm. depth was used. The cuvette was intercalated in the femoral artery of nembutalized dogs, arranged upon a board beneath the optical bench of the spectrophotometer. Clotting was prevented by previous intravenous injection of Pontamine Fast Pink and periodic injection of heparin.

A homogeneous circulation of the diverted blood flow through the very thin cuvette chamber was maintained, permitting visualization up to periods of 4 hours. The passage of blood through the cuvette was pulse-like in character (synchronous with the pulse). This did not interfere with spectrophotometry. The arrangement of connections from the artery to cuvette provided for arresting of flow through the chamber, when desired, and bypassing it through a second channel to the artery. This permitted periodic trapping of samples at opposite phases of the respiratory cycle. In these particular experiments a tracheal cannula was employed for quickly changing from room air to 100% or 10% oxygen. Samples of blood were also removed for erythrocyte count and for independent spectrophotometric analysis of hemoglobin by the usual technique with the 1 cm. cuvette upon diluted, hemolyzed blood as HbO_2, Hb (HbO_2 reduced by $Na_2S_2O_4$), and total pigment by conversion to MHbCN (cyanmethemoglobin).

Due to the presence of the anticoagulant dyestuff and lack of information concerning its level of maintenance in the blood stream, some uncertainty exists in the extrapolation of the true spectra from the data obtained in the turbid state. However, reliance may be placed upon a direct comparison of the extinction data obtained under varying conditions, and the agreement of results with those found upon hemolyzed blood, reported below. In the circulating blood, the concentration of pigment remained relatively constant (order of 5%) over a period of several hours. The percentage saturation was maintained at a level of 97 to 98%, assuming complete saturation under exposure to 100% oxygen. Samples trapped at "end expiration" showed a lower saturation (order of 2%) than corresponding samples (taken within several minutes), trapped at "end inspiration." The respiratory rate of the nembutalized animals was 10 to 12 per minute.

To avoid the use of Pontamine Fast Pink and turbid suspensions, thereby assuring full precision of spectrophotometric measurement, the following procedure was adopted. Small (6 to 15 ml. capacity) tonometers were employed as collection vessels. A solution containing 30 mg. of oxalate and 50 mg. saponin (to take care of approximately 4 ml. of blood, the size of the usual sample) was evenly air dried on the walls of the tonometer. The blood from the femoral artery of nembutalized dogs was delivered through a cannula and gum rubber connection, without contact with air, into the tonometers over clean mercury. The blood samples were collected in 3 to 4 spurts to synchronize with inspiration or expiration. By gentle shaking the blood was quickly hemolyzed. The hemolyzed sample was transferred to the 0.007 cm. cuvette, and spectrophotometry was begun within 2 to 3 minutes and completed within 6 minutes of the collection of the sample. The overflow of blood in the capillary entry and exit tubes effectively seal the chamber, so that oxygenation of the contained sample will not occur for periods of time up to 1 hour.

The rest of the sample of blood was transferred from the tonometer into a flat weighing dish. After exposure to air, portions were reread

spectrophotometrically in the 0.007 cm. cuvette with and without addition of $Na_2S_2O_4$. An aliquot was diluted and determined in the 1 cm. cuvette as HbO_2, Hb, and MHbCN (see above). Excellent agreement was obtained in all analyses. No evidence of the presence of methemoglobin or pigments other than HbO_2 and Hb could be found. The absorption spectrum of the original sample, transferred directly from the tonometer to the special 0.007 cm. cuvette agreed with that expected theoretically for the approximate mixture of HbO_2 and Hb. The percentage saturation of the saponized arterial blood of 4 dogs was high: 98.2 to 98.7 at "end inspiration," 95.5 to 96.6 at "end expiration."

The Direct Spectrophotometric Determination of the Saturation of Hemoglobin in the Arterial Blood of Man.* D. L. DRABKIN, C. F. SCHMIDT, H. D. BRUNER, and H. H. PENNES (Depts. of Physiological Chemistry and Pharmacology, and the Harrison Dept. of Surgical Research, Univ. of Penna.). The oxygen saturation of the hemoglobin of arterial blood has been determined by direct spectrophotometry in 5 male subjects, 17 to 23 years of age, 4 of them normal and 1 a controlled diabetic. Four of the subjects were non-smokers, 1 had refrained from smoking for a period of 3 days before the experiment. The arterial blood was obtained under local anesthesia by the method of femoral puncture, using cut-down lumbar puncture needles (with stilus), gauge 19. With the stilus withdrawn a free, slow flow of blood was thus provided. The needle was allowed to remain in the artery for periods of approximately 1 hour, during which time periodic samples were drawn, without contact with air, into mercury filled, saponized and oxalated tonometers (as described in the preceding report). Respiratory data were taken during blood sampling.

The analytical procedures were carried out upon the saponized samples in the manner already described. The arterial saturation proved to be uniformly high in all the individuals—98 to 99.3%. The influence of the respiratory cycle upon the arterial saturation, found in nembutalized dogs, could not be demonstrated in unanesthetized man. It is concluded that the saturation of hemoglobin in the arterial blood of man is at least 2% higher than the previously accepted value of 95% based upon the indirect gasometric technique, and which corresponds to an arterial oxygen tension at sea level (read from the dissociation curve) of the order of 75 to 80 mm. Hg. Based upon the new value for saturation an arterial oxygen tension of the order of 95 mm. may be expected.

Normal Human Arterial Oxygen Tension.* JULIUS H. COMROE, JR. (Dept. of Pharmacology, Univ. of Penna.). No agreement exists in the literature in regard to normal oxygen tension in human arterial blood; figures as high as 99 and as low as 63 mm. Hg have been recorded and the generally accepted figure is 70 to 80 mm. Hg.

The present measurements have been made using the following technique: 15 cc. of arterial blood, collected anaërobically in a syringe and heparinized, are equilibrated with 20 to 40 c.mm. of alveolar air for 10 minutes at 37° C. During this period the blood and gas tensions equalize. The gas is then transferred to a Scholander microanalyzer and the oxygen percentage and tension determined. The error of the method,

* Work done under contract with the Office of Scientific Research and Development.

determined by analyses of equilibrated bloods of known gas tension is not more than 4.5 mm. Hg.

Thirteen subjects have been used: the arterial oxygen tensions varied from 83 to 100 mm. Hg and the average tension was 93 mm. Hg. These direct measurements indicate that the arterial oxygen tension is considerably higher than heretofore believed and cast serious doubt upon the accuracy of indirect calculations of O_2 tensions (using arterial pH and O_2 saturation as determined by the Van Slyke manometric method) especially when the tensions are in the 65 to 100 mm. range, corresponding to the flat portion of the dissociation curve for oxyhemoglobin.

Preliminary Studies on Respiratory Gas Mixing With Nitrogen as a Tracer Gas.* J. C. LILLY and T. F. ANDERSON (Johnson Foundation, Univ. of Penna.). A new instrument, the nitrogen meter, is described briefly. The device continuously and rapidly records the mol fraction of nitrogen in mixtures of respiratory gases and will accurately follow a change of composition occurring in 0.02 second. Records taken on oxygen equipment at altitude are presented. A method of determining the effective gas mixing volume of the human respiratory system is described. The subject breathes pure oxygen long enough to clear his lungs of nitrogen. Next he is connected to an electrical respiratory volume recorder and the nitrogen meter, and breathes air. The resulting nitrogen record in the expiratory phase shows an initial plateau of about 70 to 125 cc. due to expired *air* diluted with water vapor, a relatively rapidly falling portion of about 100 to 150 cc., and a final plateau for the rest of the expiration. The final plateau continues at the same nitrogen concentration found in a normal expiration even with a maximal expiration. From these records the total amount of nitrogen inspired and the total amount expired have been calculated; from the difference between these 2 amounts and the concentration shown on the plateau the lung volume available for mixing is calculated. The residual volume and maximum lung volume also have been determined from these records. The method has given consistent results on 5 subjects. Possible clinical research applications are mentioned.

The Diffusion Constant of the Lung. F. J. W. ROUGHTON (Fatigue Lab., Harvard Univ. and Dept. of Physiology, Coll. of Physicians and Surgeons, Columbia Univ.). On the Diffusion Theory of gas exchange in the lungs, the volume of O_2 (cc.) which can pass through the lung per minute $= \triangle pO_2 \times DO_2$ (1)

where $\triangle pO_2$ is the average O_2 pressure difference (mm. Hg) between the alveolar air and the blood in the lung capillary. DO_2 is the diffusion constant of the whole lung to O_2.

pO_2 is calculated from the alveolar pO_2, the arterial pO_2, and the mixed venous pO_2 by Bohr's method of graphic integration (*Skand. Arch. Physiol.*, **22**, 261, 1909). DO_2 is obtained from D CO, the corresponding constant for CO as measured by Krogh's method (*J. Physiol.*, **49**, 271, 1915). Its value, in different individuals, ranges from 25 to 50 at rest and from 30 to 70 at work. It is not affected by acclimatization to high altitudes (Harrop, *Proc. Soc. Exp. Biol. and Med.*, **19**, 279, 1922).

* Work done under contract with the Office of Scientific Research and Development.

The applicability of equation (1) to work at low oxygen pressures furnishes the most crucial test of the Diffusion Theory; but unfortunately a survey of the literature (including especially the reports of the various physiologic expeditions to high altitudes) reveals only one pair of experiments in which all the necessary data are available. Asmussen and Chiodi (*Am. J. Physiol.*, **132**, 426, 1941) in their work experiments at a simulated altitude of about 20,000 feet (breathing N_2-O_2 mixtures) give the following figures: O_2 uptake per minute = 1600 cc., alveolar pO_2 = 45 mm., arterial $pO_2 = 45 \pm 2$ mm., mixed venous pO_2 = 29 mm.

From these data I calculate that $\triangle pO_2$ could not have exceeded 8 mm. at most; its exact value depends on knowing the arterial pO_2 precisely. For equation (1) to hold DO_2 must have been at least $1600 \div 8$, *i. e.*, 200—a value 3 times greater than the highest to be expected from Krogh's values for D CO. Either the Diffusion Theory is inadequate or the D CO determinations are much too low.

Haldane (*Physiol. Rev.*, **7**, 363, 1927) has questioned the validity of the D CO method on the ground of incomplete mixing of CO in the alveoli. In recent data on the rate of CO uptake when breathing air containing low per cent CO (Forbes, Sargent and Roughton, unpublished) we have, however, found values in the same range as those of Krogh. Since our experiments lasted many minutes, incomplete lung mixture could hardly have been a factor.

Another possibility is the one I advanced 20 years ago (Ph.D. Thesis, Cambridge, 1925), namely, that the assumption of zero back pressure of CO in the blood during the D CO experiments may be in error owing to the slowness of combination of CO in the red cells. On this basis the values of D CO would be too low. My calculation distinctly favored this hypothesis, which has now been put on a more experimental basis by our comparisons (Forbes and Roughton, unpublished) of the rate of uptake of CO from air and from O_2 at rest and in hard work. (The rate of chemical reaction of CO with hemoglobin varies inversely as the O_2 pressure [Roughton, *Proc. Roy. Soc.*, B, **115**, 473, 1934] and hence the back pressure of CO in the blood should be much greater when breathing O_2 than when breathing air.) At rest the substitution of O_2 for air had no effect on the rate of CO uptake but in hard work it led to a 40% reduction in the initial rate of CO uptake. These data suggest that the values of D CO at rest are correct (the back pressure of CO being negligible), but in hard work require raising by a factor of the order of 20%. Even so, a large gap remains to be closed before the results of Asmussen and Chiodi can be explained on the Diffusion Theory. Further work on these lines is therefore planned.

BOOK REVIEWS AND NOTICES

NEW BOOKS

The Psychology of Women. A Psychoanalytic Interpretation. By HELENE DEUTSCH, M.D., Associate Psychiatrist, Massachusetts General Hospital Lecturer, Boston Psychoanalytic Institute. Foreword by STANLEY COBB, M.D., Bullard Professor of Neuropathology, Harvard University. Vol. 1. Pp. 399. New York: Grune & Stratton, 1944. Price, $4.50.

The Genealogy of Gynæcology. History of the Development of Gynæcology Throughout the Ages, 2000 B.C.–1800 A.D. With excerpts from the many authors who have contributed to the various phases of the subject. By JAMES V. RICCI, A.B., M.D., Associate Clinical Professor of Gynecology and Obstetrics, New York Medical Coll.; Director of Gynecology of the City Hospital, New York; Associate Attending Gynecologist and Obstetrician, Flower and Fifth Avenue Hospitals, New York; Consultant in Gynecology and Obstetrics, Broad St. Hospital; Fellow of the New York Academy of Medicine. Pp. 578; 54 figs. Philadelphia: Blakiston, 1943. Price, $8.50.

Tuberculosis of the Ear, Nose, and Throat: Including The Larynx, The Trachea, and The Bronchi. By MERVIN C. MYERSON, M.D. Dedication to DOCTOR HUBERT ARROWSMITH, Pioneer in Bronchoscopy and Laryngology. An outstanding worker in the field of tuberculosis. Pp. 291; 89 figs. Springfield, Ill.: Charles C Thomas, 1944. Price, $5.50.

Manual of Human Protozoa. By RICHARD R. KUDO, D.Sc., Associate Professor of Zoölogy, Univ. of Illinois. Pp. 125; 29 figs. Springfield, Ill.: Charles C Thomas, 1944. Price, $2.00.

Intercranial Arterial Aneurysms. By WALTER E. DANDY, Adjunct Professor of Surgery in Johns Hopkins University. Pp. 147; 55 figs.; 5 tables. Ithaca, N. Y.: Comstock Pub. Co., Cornell Univ., 1944. Price, $2.50.

Æsculapius in Latin America. By ARISTIDES A. MOLL, PH.D., Secretary-Editor of the Pan-American Sanitary Bureau, Washington, D. C.; Consultant in Tropical Medicine to the Secretary of War; Honorary Professor of the Port-au-Prince Medical School; Former Editor of the Spanish Ed. of the *Journal of the American Medical Association;* Secretary (1933–1940) of the Pan-American Medical Association (Washington, D. C.); Secretary of the Tenth and Eleventh Pan-American Sanitary Conferences and the Second, Third and Fourth Pan-American Conferences of National Directors of Health; Decorated by the Governments of Chile, Columbia, Cuba, Ecuador and Haiti. Pp. 639. Numerous illus. Philadelphia and London: W. B. Saunders, 1944. Price, $7.00.

Practical Malaria Control. A Handbook for Field Workers. By CARL E. M. GUNTHER, M.D., B.S., D.T.M. (SYDNEY), Field Medical Officer, Bulolo Gold Dredging Limited, Territory of New Guinea, at present with the Australian Medical Corps. Foreword by PROF. HARVEY SUTTON, O.B.E., M.D., F.R.A.C.P., B.Sc., D.P.H., F.R. SAN. I. Pp. 91. New York: Philosophical Library, 1944. Price, $2.50.

Systematic Inorganic Chemistry. Of the Fifth-And-Sixth-Group Nonmetallic Elements. By DON M. YOST, Professor of Inorganic Chemistry, California Institute of Technology; and HORACE RUSSELL, JR., Instructor in Chemistry, California Institute of Technology. Dedication to WILLIAM C. BRAY, Able Scientist, Inspiring Teacher. Pp. 423; 78 figs. New York: Prentice-Hall, 1944. Price, $4.60.

XUM

The Diet Therapy of Disease. A Handbook of Practical Nutrition. By LOUIS PELNER, M.D., Assistant Attending Physician, Long Island Hospital, Greenpoint Hospital, and Brooklyn Cancer Institute; Gastroscopist, Beth Moses Hospital; Lecturer, Post-Graduate Course in Gastro-enterology, under charge of Dr. S. A. Seley. Pp. 143. New York; Personnel Diet Service, 1944. Price, $3.75.

Intravenous Anesthesia. By R. CHARLES ADAMS, M.D., C.M., M.S. (ANES.), Associate in Section on Anesthesiology, Mayo Clinic; Instructor in Anesthesiology, Mayo Foundation for Medical Education and Research, Graduate School Univ. of Minnesota, Rochester, Minn. Dedication to DR. JOHN S. LUNDY, Friend and Teacher. Foreword by DR. JOHN S. LUNDY. Pp. 663; 34 tables; 75 figs. New York and London: Paul B. Hoeber, 1944. Price, $12.00.

One Hundred Years of American Psychiatry. Published for the American Psychiatric Association. By the following Contributors: HENRY ALDEN BUNKER, ALBERT DEUTSCH, J. K. HALL, SAMUEL W. HAMILTON, CLYDE KLUCKHOHN, WILLIAM MALAMUD, DOM THOMAS VERNER MOORE, WINFRED OVERHOLSER, RICHARD H. SHRYOCK, HENRY E. SIGERIST, EDWARD A. STRECKER, JOHN C. WHITEHORN, GREGORY ZILBOORG. Pp. 649; 35 illus. New York: Columbia Univ. Press, 1944. Price, $6.00.

The Management of Neurosyphilis. By BERNHARD DATTNER, M.D., JUR.D., Associate Clinical Professor of Neurology, New York Univ. Medical Coll. With the collaboration of EVAN W. THOMAS, M.D. Foreword by JOSEPH EARLE MOORE, M.D. Pp. 398; 40 figs.; charts, tables. New York: Grune & Stratton, 1944. Price, $5.50.

The Treatment of Peptic Ulcer. Based Upon Ten Years' Experience at the New York Hospital. By GEORGE J. HEUER, M.D., Professor of Surgery of Cornell Univ. Medical Coll. and Surgeon-in-Chief of the New York Hospital. Assisted by CRANSTON HOLMAN, M.D., Assistant Professor of Clinical Surgery, Cornell Univ. Medical Coll., and WILLIAM A. COOPER, M.D., Assistant Professor of Clinical Surgery, Cornell Univ. Medical Coll. Pp. 118. Philadelphia: J. B. Lippincott, 1944. Price, $3.00.

Technique in Trauma. Planned Timing in the Treatment of Wounds Including Burns. From the Montreal General Hospital and McGill Univ. By FRASER B. GURD, M.D., C.M., and F. DOUGLAS ACKMAN, M.D., C.M. In collaboration with JOHN W. GERRIE, M.D., C.M., EDWARD S. MILLS, M.D., C.M., JOSEPH E. PRITCHARD, M.D., FREDERICK SMITH, M.D. Preface by JOHN S. LOCKWOOD, M.D., Univ. of Pennsylvania; and Commentary by RALPH R. FITZGERALD, M.D., C.M., McGill Univ. Pp. 68; 17 figs.; 5 tables; 3 charts; 3 color plates. Philadelphia: J. B. Lippincott, 1944. Price, $2.00.

Radiation and Climatic Therapy of Chronic Pulmonary Diseases. With Special Reference to Natural and Artificial Heliotherapy, *X*-ray Therapy, and Climatic Therapy of Chronic Pulmonary Diseases and All Forms of Tuberculosis. Edited by EDGAR MAYER, M.D., F.A.C.P., F.A.C.C.P., and 22 Collaborators. Pp. 393; 46 figs.; 15 tables. Baltimore: Williams & Wilkins, 1944. Price, $5.00.

NEW EDITIONS

A Manual of Physical Therapy. Formerly published under the title "Physical Therapy for Nurses." By RICHARD KOVACS, M.D., Professor of Physical Therapy, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State, Columbus, and West Side Hospitals, New York. Third ed. Pp. 309; 29 tables; 118 figs.; 118 illus. Philadelphia: Lea & Febiger, 1944. Price, $3.25.

Functional Disorders of the Foot. Their Diagnosis and Treatment. By FRANK D. DICKSON, M.D., F.A.C.S., Associate Professor of Clinical Surgery, Medical School, Univ. of Kansas; Orthopedic Surgeon, St. Luke's, Kansas City General, and Wheatley Hospitals, Kansas City, Mo.; Providence Hospital, Kansas City, Kan.; and REX L. DIVELEY, A.B., M.D., F.A.C.S., Colonel, Medical Corps, A.U.S.; Orthopedic Consultant, European Theater of Operations; Orthopedic Surgeon, St. Luke's Hospital, Kansas City, Kan. Second ed. Pp. 352; 202 figs. Philadelphia: J. B. Lippincott, 1944. Price, $5.00.

Fundamentals of Psychiatry. By EDWARD A. STRECKER, M.D., Sc.D., F.A.C.P. Professor of Psychiatry and Chairman of the Department, Undergraduate School of Medicine, Univ. of Pennsylvania; Psychiatrist to the Pennsylvania Hospital; Attending Psychiatrist, Psychopathic Division, Philadelphia General Hospital; Consultant to the Bureau of Medicine and Surgery, U.S.N.; Consultant to the Secretary of War, A.A.F. Second ed. Pp. 219; 15 figs. Philadelphia, London and Montreal: J. B. Lippincott, 1944. Price, $3.00.

BACTERIAL INFECTION. With Special Reference to Dental Practice. By J. L. T. APPLETON, B.S., D.D.S., Sc.D., Professor of Bacteriopathology and Dean, The Thomas W. Evans Museum and Dental Institute School of Dentistry, Univ. of Pennsylvania. Third ed. Pp. 498; 86 figs.; 5 color plates. Philadelphia: Lea & Febiger, 1944. Price, $7.00.

The American Illustrated Medical Dictionary. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Lieut. Colonel, M.R.C., U.S.A.; Member of the Committee on Nomenclature and Classification of Diseases of the American Medical Association; Editor of "American Pocket Medical Dictionary." With the collaboration of E. C. L. MILLER, M.D., Medical College of Virginia. Twentieth ed. Pp. 1668; 885 illus.; 240 portraits. Philadelphia and London: W. B. Saunders, 1944. Price, plain—$7.00; thumb-indexed—$7.50.

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